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<p>(54) Title: KETOHETEROCYCLIC INHIBITORS OF FACTOR Xa</p> <p>(57) Abstract</p> <p>Novel compounds, their salts and compositions related thereto having activity against mammalian factor Xa are disclosed. The compounds are useful <i>in vitro</i> or <i>in vivo</i> for preventing or treating coagulation disorders.</p>			

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KETOHETEROCYCLIC INHIBITORS OF FACTOR Xa

Field of the Invention

10 This invention relates to novel ketoheterocyclic-containing compounds which are potent and highly selective inhibitors of isolated factor Xa or when assembled in the prothrombinase complex. In another aspect, the present invention relates to novel peptide and peptide mimetic analogs, their pharmaceutically acceptable salts, and pharmaceutically acceptable compositions thereof which are useful as potent
15 and specific inhibitors of blood coagulation in mammals. In yet another aspect, the invention relates to methods for using these inhibitors as therapeutic agents for disease states in mammals characterized by coagulation disorders.

Background of the Invention

20 Hemostasis, the control of bleeding, occurs by surgical means, or by the physiological properties of vasoconstriction and coagulation. This invention is particularly concerned with blood coagulation and ways in which it assists in maintaining the integrity of mammalian circulation after injury, inflammation, disease, congenital defect, dysfunction or other disruption. Under normal hemostatic
25 circumstances, the body maintains an acute balance of clot formation and clot removal (fibrinolysis). The blood coagulation cascade involves the conversion of a variety of inactive enzymes (zymogens) into active enzymes which ultimately convert the soluble plasma protein fibrinogen into an insoluble matrix of highly cross-linked fibrin, Davie, E.J. *et al.*, "The Coagulation Cascade: Initiation, Maintenance and
30 Regulation", Biochemistry, 30, 10363-10370 (1991). These plasma glycoprotein zymogens include Factor XII, Factor XI, Factor IX, Factor X, Factor VII, and prothrombin. Blood coagulation follows either the intrinsic pathway, where all of the protein components are present in blood, or the extrinsic pathway, where the cell-membrane protein tissue factor plays a critical role. Clot formation occurs when
35 fibrinogen is cleaved by thrombin to form fibrin. Blood clots are composed of activated platelets and fibrin.

Blood platelets which adhere to damaged blood vessels are activated and incorporated into the clot and thus play a major role in the initial formation and stabilization of hemostatic "plugs". In certain diseases of the cardiovascular system,
40 deviations from normal hemostasis push the balance of clot formation and clot

5 dissolution towards life-threatening thrombus formation when thrombi occlude blood flow in coronary vessels (myocardial infarctions) or limb and pulmonary veins (venous thrombosis). Although platelets and blood coagulation are both involved in thrombus formation, certain components of the coagulation cascade are primarily responsible for the amplification or acceleration of the processes involved in platelet 10 aggregation and fibrin deposition.

Thrombin is a key enzyme in the coagulation cascade as well as in hemostasis. Thrombin plays a central role in thrombosis through its ability to catalyze the conversion of fibrinogen into fibrin and through its potent platelet activation activity. Under normal circumstances, thrombin can also play an 15 anticoagulant role in hemostasis through its ability to convert protein C into activated protein C (aPC) in a thrombomodulin-dependent manner. However, in atherosclerotic arteries these thrombin activities can initiate the formation of a thrombus, which is a major factor in pathogenesis of vasoocclusive conditions such as myocardial infarction, unstable angina, nonhemorrhagic 20 stroke and reocclusion of coronary arteries after angioplasty or thrombolytic therapy. Thrombin is also a potent inducer of smooth muscle cell proliferation and may therefore be involved in a variety of proliferative responses such as restenosis after angioplasty and graft induced atherosclerosis. In addition, thrombin is chemotactic for leukocytes and may therefore play a role in 25 inflammation. (Hoover, R.J., et al. *Cell*, 14, 423 (1978); Etingin, O.R., et al., *Cell*, 61, 657 (1990). These observations indicate that inhibition of thrombin formation or inhibition of thrombin itself may be effective in preventing or treating thrombosis, limiting restenosis and controlling inflammation.

30 Direct or indirect inhibition of thrombin activity has been the focus of a variety of recent anticoagulant strategies as reviewed by Claeson, G., "Synthetic Peptides and Peptidomimetics as Substrates and Inhibitors of Thrombin and Other Proteases in the Blood Coagulation System", *Blood Coag. Fibrinol.* 5, 411-436 (1994). Several classes of anticoagulants currently used in the clinic directly or indirectly affect 35 thrombin (i.e. heparins, low-molecular weight heparins, heparin-like compounds and coumarins).

The formation of thrombin is the result of the proteolytic cleavage of its precursor prothrombin at the Arg-Thr linkage at positions 271-272 and the Arg-Ile linkage at positions 320-321. This activation is catalyzed by the prothrombinase complex, which is assembled on the membrane surfaces of platelets, monocytes,

5 and endothelial cells. The complex consists of Factor Xa (a serine protease), Factor Va (a cofactor), calcium ions and the acidic phospholipid surface. Factor Xa is the activated form of its precursor, Factor X, which is secreted by the liver as a 58 kd precursor and is converted to the active form, Factor Xa, in both the extrinsic and intrinsic blood coagulation pathways. Factor X is a member of the calcium ion binding, gamma carboxyglutamyl (Gla)-containing, vitamin K dependent, blood coagulation glycoprotein family, which also includes Factors VII and IX, prothrombin, protein C and protein S (Furie, B., et al., Cell, 53, 505 (1988)). The activity of Factor Xa in effecting the conversion of prothrombin to thrombin is dependent on its inclusion in the prothrombinase complex.

10 15 The prothrombinase complex converts the zymogen prothrombin into the active procoagulant thrombin. It is therefore understood that Factor Xa catalyzes the next-to-last step in the blood coagulation cascade, namely the formation of the serine protease thrombin. In turn, thrombin then acts to cleave soluble fibrinogen in the plasma to form insoluble fibrin.

20 25 The location of the prothrombinase complex at the convergence of the intrinsic and extrinsic coagulation pathways, and the resulting significant amplification of thrombin generation (several hundred-thousand fold faster in effecting the conversion of prothrombin to thrombin than Factor Xa in soluble form) mediated by the complex at a limited number of targeted catalytic units present at vascular lesion sites, suggests that inhibition of thrombin generation is a desirable method to block uncontrolled procoagulant activity. It has been suggested that compounds which selectively inhibit factor Xa may be useful as *in vitro* diagnostic agents, or for therapeutic administration in certain thrombotic disorders, see e.g., WO 94/13693. Unlike thrombin, which acts on a variety of protein substrates as well

30 35 as at a specific receptor, factor Xa appears to have a single physiologic substrate, namely prothrombin.

Plasma contains an endogenous inhibitor of both the factor VIIa-tissue factor (TF) complex and factor Xa called tissue factor pathway inhibitor (TFPI). TFPI is a Kunitz-type protease inhibitor with three tandem Kunitz domains. TFPI inhibits the TF/fVIIa complex in a two-step mechanism which includes the initial interaction of the second Kunitz domain of TFPI with the active site of factor Xa, thereby inhibiting the proteolytic activity of factor Xa. The second step involves the inhibition of the TF/fVIIa complex by formation of a quaternary complex TF/fVIIa/TFPI/fXa as described by Girard, T.J. et al., "Functional Significance of the Kunitz-type Inhibitory

5 Domains of Lipoprotein-associated Coagulation Inhibitor^a, *Nature*, 338, 518-520
(1989).

Polypeptides derived from hematophagous organisms have been reported which are highly potent and specific inhibitors of factor Xa. United States Patent 4,588,587 describes anticoagulant activity in the saliva of the Mexican leech,

10 *Haementeria officinalis*. A principal component of this saliva was shown to be the polypeptide factor Xa inhibitor, antistasin (ATS), by Nutt, E. et al., "The Amino Acid Sequence of Antistasin, a Potent Inhibitor of Factor Xa Reveals a Repeated Internal Structure", *J. Biol. Chem.*, 263, 10162-10167 (1988).

Another potent and highly specific inhibitor of Factor Xa, called tick
15 anticoagulant peptide (TAP), has been isolated from the whole body extract of the soft tick *Ornithodoros moubata*, as reported by Waxman, L., et al., "Tick Anticoagulant Peptide (TAP) is a Novel Inhibitor of Blood Coagulation Factor Xa" *Science*, 248, 593-596 (1990).

Other polypeptide type inhibitors of factor Xa have been reported including
20 the following: Condra, C. et al., "Isolation and Structural Characterization of a Potent Inhibitor of Coagulation Factor Xa from the Leech *Haementeria ghilianii*", *Thromb. Haemost.*, 61, 437-441 (1989); Blankenship, D.T. et al., "Amino Acid Sequence of Ghilanten: Anti-coagulant-antimetastatic Principle of the South American Leech, *Haementeria ghilianii*", *Biochem. Biophys. Res. Commun.* 166, 1384-1389 (1990);
25 Brankamp, R.G. et al., "Ghilantens: Anticoagulants, Antimetastatic Proteins from the South American Leech *Haementeria ghilianii*", *J. Lab. Clin. Med.*, 115, 89-97 (1990); Jacobs, J.W. et al., "Isolation and Characterization of a Coagulation Factor Xa Inhibitor from Black Fly Salivary Glands", *Thromb. Haemost.*, 64, 235-238 (1990); Rigbi, M. et al., "Bovine Factor Xa Inhibiting Factor and Pharmaceutical
30 Compositions Containing the Same", European Patent Application, 352,903; Cox, A.C., "Coagulation Factor X Inhibitor From the Hundred-pace Snake *Deinagkistrodon acutus*, venom", *Toxicon*, 31, 1445-1457 (1993); Cappello, M. et al., "Ancylostoma Factor Xa Inhibitor: Partial Purification and its Identification as a Major Hookworm-derived Anticoagulant In Vitro", *J. Infect. Dis.*, 167, 1474-1477 (1993); Seymour, J.L.
35 et. al., "Ecotin is a Potent Anticoagulant and Reversible Tight-binding Inhibitor of Factor Xa", *Biochemistry* 33, 3949-3958 (1994).

Factor Xa inhibitory compounds which are not large polypeptide-type inhibitors have also been reported including: Tidwell, R.R. et al., "Strategies for Anticoagulation With Synthetic Protease Inhibitors. Xa Inhibitors Versus Thrombin

5 Inhibitors", *Thromb. Res.*, 19, 339-349 (1980); Turner, A.D. *et al.*, "p-Amidino Esters as Irreversible Inhibitors of Factor IXa and Xa and Thrombin", *Biochemistry*, 25, 4929-4935 (1986); Hitomi, Y. *et al.*, "Inhibitory Effect of New Synthetic Protease Inhibitor (FUT-175) on the Coagulation System", *Haemostasis*, 15, 164-168 (1985); Sturzebecher, J. *et al.*, "Synthetic Inhibitors of Bovine Factor Xa and Thrombin.

10 Comparison of Their Anticoagulant Efficiency", *Thromb. Res.*, 54, 245-252 (1989); Kam, C.M. *et al.*, "Mechanism Based Isocoumarin Inhibitors for Trypsin and Blood Coagulation Serine Proteases: New Anticoagulants", *Biochemistry*, 27, 2547-2557 (1988); Hauptmann, J. *et al.*, "Comparison of the Anticoagulant and Antithrombotic Effects of Synthetic Thrombin and Factor Xa Inhibitors", *Thromb. Haemost.*, 63, 220-223 (1990); Miyadera, A. *et al.*, Japanese Patent Application JP 6327488; Nagahara, T. *et al.*, "Dibasic (Amidinoaryl)propanoic Acid Derivatives as Novel Blood Coagulation Factor Xa Inhibitors", *J. Med. Chem.*, 37, 1200-1207 (1994); Vlasuk, G.P. *et al.*, "Inhibitors of Thrombosis", WO 93/15756; and Brunck, T.K. *et al.*, "Novel Inhibitors of Factor Xa", WO 94/13693.

20 A number of inhibitors of trypsin-like enzymes (such as trypsin, enterokinase, thrombin, kallikrein, plasmin, urokinase, plasminogen activators and the like) have been the subject of disclosures. For example, Austen *et al.*, United States Patent 4,593,018 describes oligopeptide aldehydes which are specific inhibitors of enterokinase; Abe *et al.*, United States Patent 5,153,176 describes tripeptide aldehydes which have inhibitory activity against multiple serine proteases such as plasmin, thrombin, trypsin, kallikrein, factor Xa, urokinase, etc.; Brunck *et al.*, European Publication WO 93/14779 describes substituted tripeptide aldehydes that are specific inhibitors of trypsin; United States Patents 4,316889, United States Patent 4,399,065, United States Patent 4,478,745 all disclose arginine aldehyde inhibitors of thrombin; Balasubramanian *et al.*, United States Patent 5,380,713 describes di and tripeptide aldehydes which are useful for anti-trypsin and anti-thrombin activity; Webb *et al.*, United States Patent 5,371,072 describes tripeptide alpha-keto-amide derivatives as inhibitors of thrombosis and thrombin; Gesellchen *et al.*, European Patent Publications 0479489A2 and 0643073 A, describe tripeptide thrombin inhibitors; Veber *et al.*, European Publication WO 94/25051 describes 4-cyclohexylamine derivatives which selectively inhibit thrombin over other trypsin-like enzymes; Tapparelli *et al.*, *J. Biol. Chem.* 268, 4734-4741 (1993) describe selective peptide boronic acid derivatives as inhibitors of thrombin.

5 Alternatively, agents which inhibit the vitamin K-dependent carboxylase enzyme, such as coumarin, have been used to treat coagulation disorders.

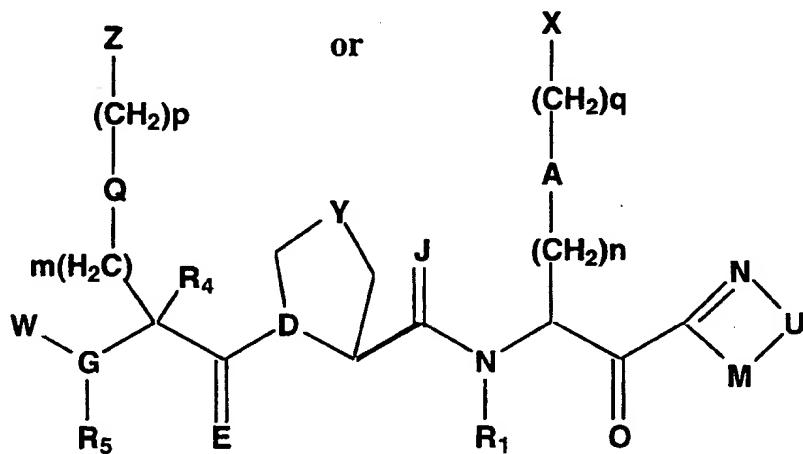
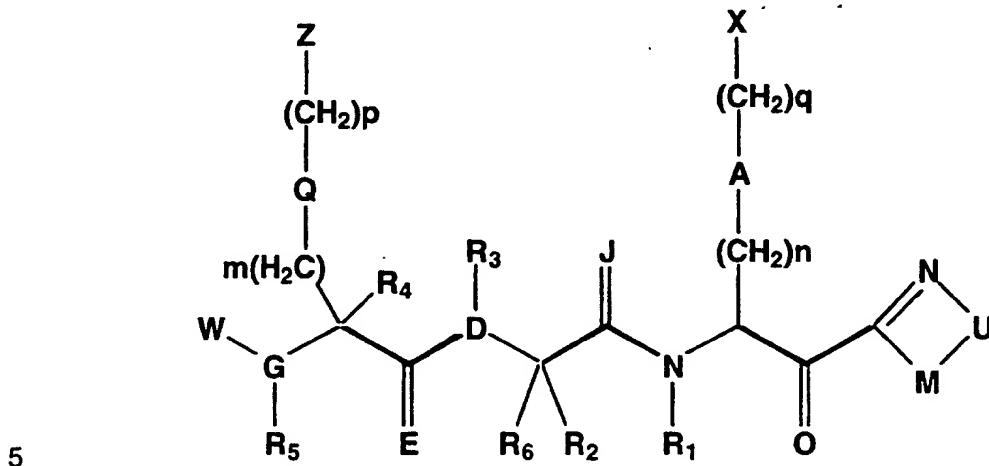
10 There exists a need for effective therapeutic agents for the regulation of hemostasis, and for the prevention and treatment of thrombus formation and other pathological processes in the vasculature induced by thrombin such as restenosis and inflammation.

Summary of the Invention

The present invention relates to novel peptide and peptide mimetic analogs, their pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives, and pharmaceutically acceptable compositions thereof which have particular biological properties and are useful as potent and specific inhibitors of blood coagulation in mammals. In another aspect, the invention relates to methods of using these inhibitors as diagnostic reagents or as therapeutic agents for disease states in mammals which have coagulation disorders, such as in the treatment or prevention of any thrombotically mediated acute coronary or cerebrovascular syndrome, any thrombotic syndrome occurring in the venous system, any coagulopathy, and any thrombotic complications associated with extracorporeal circulation or instrumentation, and for the inhibition of coagulation in biological samples.

25 In certain embodiments, this invention relates to novel arginine and arginine mimetic-containing compounds which are potent and highly selective inhibitors of isolated factor Xa when assembled in the prothrombinase complex. These compounds show selectivity for factor Xa versus other proteases of the coagulation cascade (e.g. thrombin, etc.) or the fibrinolytic cascade, and are useful as diagnostic reagents as well as antithrombotic agents.

30 In preferred embodiments, the present invention provides compounds of the formula:



wherein:

10 m = 0,1,2,3,4;
 n = 0,1,2,3,4;
 p = 0,1,2,3,4;
 q = 0,1,2,3,4;
 Y = NH, S, O, CH₂, CH-OH, CH₂CH₂, C=O;

15 A = piperdinyl, pyrrolidinyl, cyclopropyl, cyclobutyl, cyclopentyl,
 cyclohexyl, phenyl, C₃₋₆heteroaryl, or is absent;
 R₁ = H or C₁₋₃alkyl;
 J = O or H₂;

20 R₂ = H or C₁₋₃alkyl;
 D = N, CH, NCH₂, NCH₂CH₂, CHCH₂;
 R₃ = H or C₁₋₃alkyl;

5 E = O or H₂;

R₄ = H or CH₃;

M = NH, N-CH₃, O, S, SO, SO₂ or CH₂ or is absent;

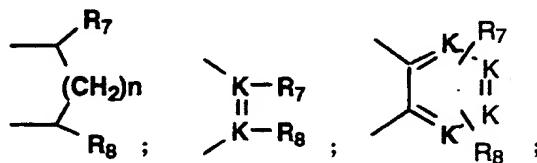
Q = piperdanyl, pyrrolidinyl, C₃-8 cycloalkyl, phenyl, substituted phenyl, naphthyl, pyridyl, or is absent;

10 G = N, CH, or H;

R₅ = H or C₁-3 alkyl or is absent if G is H;

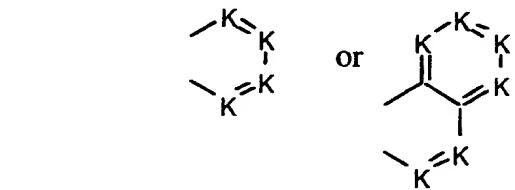
R₆ = H or CH₃;

U = is selected from the group consisting of



15 where n = 0-4; R₇ and R₈ are independently selected from a group consisting of H, C₁-10alkyl, aryl, arylalkyl, halogen, nitro, an amino group of formula -NR₉R₁₀, an acylamino group of formula -NHCOR₁₁, hydroxy, an acyloxy group of formula -OCOR₁₂, C₁-4alkyloxy, C₁-4alkyl, trifluoromethyl, carboxy, cyano, phenyl, an aromatic heterocyclic group, C₁-4alkyloxycarbonyl, an aminocarbonyl group of formula CONR₁₃R₁₄, sulfo, sulfonamido of formula SO₂NR₁₅R₁₆ and C₁-6 hydroxyalkyl, wherein R₉, R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆ are the same or different and = H, C₁-6 alkyl, C₁-3arylalkyl or aryl; and if M is absent:

20 25



K = C or N;

W = H, arylacyl, heteroarylacyl, arylC₁-3alkylsulfonyl, arylsulfonyl, substituted arylsulfonyl, arylC₁-4alkenylsulfonyl, C₁-8 alkylsulfonyl, heteroarylC₁-3alkylsulfonyl, heteroarylisulfonyl, aryloxycarbonyl, C₁-6 alkyloxycarbonyl, arylC₁-

30

5 3alkyloxycarbonyl, arylaminocarbonyl, C₁-6alkylaminocarbonyl, aryC₁-3alkylaminocarbonyl, HOOC-C₀-3alkylcarbonyl, or is absent if G is H;

X = H,C₁₋₃alkyl, NR'R'', NH-C(NR'R'')=NH, NH-C(NHR')=NR'', NH-C(R')=NR'', S-C(NR'R'')=NH, S-C(NHR')=NR'', C(NR'R'')=NH, C(NHR')=NR'', or CR'=NR''; where: R',R'' are the same or different and = H, C₁-6alkyl, C₁-3arylalkyl, aryl or where R'R'' forms a cyclic ring containing (CH₂)_p where p=2-5, with the proviso that when X is H or C₁₋₃alkyl, then A must contain at least one N atom;

10 Z = H, C₁₋₃alkyl, NR'R'', NH-C(NR'R'')=NH, NH-C(NHR')=NR'', NH-C(R')=NR'', S-C(NR'R'')=NH, S-C(NHR')=NR'', C(NR'R'')=NH, C(NHR')=NR'', or CR'=NR''; where: R',R'' are the same or different and = H, C₁-6alkyl, C₁-3arylalkyl, aryl or where R'R'' forms a cyclic ring containing (CH₂)_p where p=2-5, with the proviso that when Z is H or C₁₋₃alkyl, then Q must contain at least one N atom;

15 20 and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In certain aspects of this invention, compounds are provided which are useful as diagnostic reagents. In another aspect, the present invention includes pharmaceutical compositions comprising a pharmaceutically effective amount of the compounds of this invention and a pharmaceutically acceptable carrier. In yet another aspect, the present invention includes methods comprising using the above compounds and pharmaceutical compositions for preventing or treating disease states characterized by disorders of the blood coagulation process in mammals, or for preventing coagulation in stored blood products and samples. Optionally, the methods of this invention comprise administering the pharmaceutical composition in combination with an additional therapeutic agent such as an antithrombotic and/or a thrombolytic agent and/or an anticoagulant.

30 35 The preferred compounds also include their pharmaceutically acceptable isomers, hydrates, solvates, salts and prodrug derivatives.

5

Detailed Description of the InventionDefinitions

In accordance with the present invention and as used herein, the following terms are defined with the following meanings, unless explicitly stated otherwise.

The term "alkenyl" refers to a trivalent straight chain or branched chain
10 unsaturated aliphatic radical.

The term "alkyl" refers to saturated aliphatic groups including straight-chain, branched-chain and cyclic groups having the number of carbon atoms specified, or if no number is specified, having up to 12 carbon atoms. The term "cycloalkyl" as used herein refers to a mono-, bi-, or tricyclic aliphatic ring having 3 to 14 carbon atoms
15 and preferably 3 to 7 carbon atoms.

The term "aryl" refers to an unsubstituted or substituted aromatic ring, substituted with one, two or three substituents selected from loweralkoxy, loweralkyl, loweralkylamino, hydroxy, halogen, cyano, hydroxyl, mercapto, nitro, thioalkoxy, carboxaldehyde, carboxyl, carboalkoxy and carboxamide, including but not limited to
20 carbocyclic aryl, heterocyclic aryl, and biaryl groups and the like, all of which may be optionally substituted. Preferred aryl groups include phenyl, halophenyl, loweralkylphenyl, naphthyl, biphenyl, phenanthrenyl, naphthacenyl, and aromatic heterocyclics. The term "heteroaryl" as used herein refers to any aryl group, containing from one to four heteroatoms, selected from the group consisting of
25 nitrogen, oxygen and sulfur.

The term "arylalkyl" refers to one, two, or three aryl groups having the number of carbon atoms designated, appended to an alkyl group having the number of carbon atoms designated. Suitable arylalkyl groups include, but are not limited to, benzyl, picolyl, naphthylmethyl, phenethyl, benzyhydryl, trityl, and the like, all of
30 which may be optionally substituted.

The terms "halo" or "halogen" as used herein refer to Cl, Br, F or I substituents.

The term "methylene" refers to -CH₂-.

The term "pharmaceutically acceptable salts" includes salts of compounds
35 derived from the combination of a compound and an organic or inorganic acid. These compounds are useful in both free base and salt form. In practice, the use of the salt form amounts to use of the base form; both acid and base addition salts are within the scope of the present invention.

5 "Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid,

10 oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

"Pharmaceutically acceptable base addition salts" include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Salts derived from pharmaceutically acceptable organic nontoxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins and the like. Particularly preferred organic nontoxic bases are isopropylamine, diethylamine, ethanolamine, trimethamine, dicyclohexylamine, choline, and caffeine.

"Biological property" for the purposes herein means an *in vivo* effector or antigenic function or activity that is directly or indirectly performed by a compound of this invention. Effector functions include receptor or ligand binding, any enzyme activity or enzyme modulatory activity, any carrier binding activity, any hormonal activity, any activity in promoting or inhibiting adhesion of cells to an extracellular matrix or cell surface molecules, or any structural role. Antigenic functions include possession of an epitope or antigenic site that is capable of reacting with antibodies raised against it.

35 The nomenclature used to describe the peptide compounds of the invention follows the conventional practice where the N-terminal amino group is assumed to be to the left and the carboxy group to the right of each amino acid residue in the peptide. In the formulas representing selected specific embodiments of the present invention, the amino- and carboxy-terminal groups, although often not specifically

5 shown, will be understood to be in the form they would assume at physiological pH values, unless otherwise specified. Thus, the N-terminal H⁺ and C-terminal O⁻ at physiological pH are understood to be present though not necessarily specified and shown, either in specific examples or in generic formulas. Free functional groups on the side chains of the amino acid residues can also be modified by amidation, 10 acylation or other substitution, which can, for example, change the solubility of the compounds without affecting their activity.

In the peptides described herein, each gene-encoded residue, where appropriate, is represented by a single letter designation, corresponding to the trivial name of the amino acid, in accordance with the following conventional list:

15

		One-Letter	Three-letter
	<u>Amino Acid</u>	<u>Symbol</u>	<u>Symbol</u>
	Alanine	A	Ala
	Arginine	R	Arg
20	Asparagine	N	Asn
	Aspartic acid	D	Asp
	Cysteine	C	Cys
	Glutamine	Q	Gln
	Glutamic acid	E	Glu
25	Glycine	G	Gly
	Histidine	H	His
	Isoleucine	I	Ile
	Leucine	L	Leu
	Lysine	K	Lys
30	Methionine	M	Met
	Phenylalanine	F	Phe
	Proline	P	Pro
	Serine	S	Ser
	Threonine	T	Thr
35	Tryptophan	W	Trp
	Tyrosine	Y	Tyr
	Valine	V	Val

In addition, the following abbreviations are used in this application:

5 "Ala" refers to L-Alanine.
 "D-Ala" refers to D-Alanine.
 "Arg" refers to L-Arginine.
 "D-Arg" refers to D-Arginine.
 "Bn" refers to benzyl.
10 "t-Boc" refers to t-butoxycarbonyl.
 "BOP" refers to benzotriazol-1-yloxy-tris-(dimethylamino)phosphonium
 hexafluorophosphate.
 "Cbz" refers to benzyloxycarbonyl.
 "DCM" refers to dichloromethane.
15 "DIEA" refers to diisopropylethylamine.
 "DMF" refers to N,N-dimethylformamide.
 "EDC" refers to ethyl-3-(3-dimethylamino)-propyl carbodiimide•HCL
 "EtOAc" refers to ethyl acetate.
 "Gly" refers to glycine.
20 "HOSu" refers to N-hydroxysuccinimide.
 "D-Lys" refers to D-Lysine.
 "MeOH" refers to methanol.
 "MeSEt" refers to methyl ethyl sulfide.
 "NaOAc" refers to sodium acetate.
25 "Ph" refers to phenyl.
 "D-Pro" refers to D-proline.
 "Pro" refers to L-proline.
 "TEA" refers to triethylamine.
 "TFA" refers to trifluoroacetic acid.
30 "THF" refers to tetrahydrofuran.
 "Tos" refers to p-toluenesulfonyl.

The amino acids not encoded genetically are abbreviated as described above or have the meanings commonly accepted in the field.

In the compounds of this invention, carbon atoms bonded to four non-
35 identical substituents are asymmetric. Accordingly, the compounds may exist as diastereoisomers, enantiomers or mixtures thereof. The syntheses described herein may employ racemates, enantiomers or diastereomers as starting materials or intermediates. Diastereomeric products resulting from such syntheses may be separated by chromatographic or crystallization methods, or by other methods

5 known in the art. Likewise, enantiomeric product mixtures may be separated using the same techniques or by other methods known in the art. Each of the asymmetric carbon atoms, when present in the compounds of this invention, may be in one of two configurations (R or S) and both are within the scope of the present invention. In certain specified preferred embodiments of the compounds shown in the present

10 application, the L-form of any amino acid residue having an optical isomer is intended unless the D-form is expressly indicated. In the processes described above, the final products may, in some cases, contain a small amount of the products having D or L-form residues, however these products do not affect their therapeutic or diagnostic application.

15 The compounds of the invention are peptides or compounds which contain amino acid subunits which are partially defined in terms of amino acid residues of designated classes. Amino acid residues can be generally grouped into four major subclasses as follows:

Acidic: The residue has a negative charge due to loss of H ion at physiological pH and the residue is attracted by aqueous solution.

20 Basic: The residue has a positive charge due to association with H ion at physiological pH and the residue is attracted by aqueous solution.

Neutral/nonpolar: The residues are not charged at physiological pH and the residue is repelled by aqueous solution so as to seek the inner positions in the 25 conformation of a peptide in which it is contained when the peptide is in aqueous medium. These residues are also designated "hydrophobic" herein.

Neutral/polar: The residues are not charged at physiological pH, but the residue is attracted by aqueous solution so as to seek the outer positions in the conformation of a peptide in which it is contained when the peptide is in aqueous 30 medium.

It is understood, of course, that in a statistical collection of individual residue molecules some molecules will be charged, and some not, and there will be an attraction for or repulsion from an aqueous medium to a greater or lesser extent. To fit the definition of "charged," a significant percentage (at least approximately 25%) 35 of the individual molecules are charged at physiological pH. The degree of attraction or repulsion required for classification as polar or nonpolar is arbitrary and, therefore, amino acids specifically contemplated by the invention have been classified as one or the other. Most amino acids not specifically named can be classified on the basis of known behavior.

5 Amino acid residues can be further subclassified as cyclic or noncyclic, and aromatic or nonaromatic, self-explanatory classifications with respect to the side chain substituent groups of the residues, and as small or large. The residue is considered small if it contains a total of 4 carbon atoms or less, inclusive of the carboxyl carbon. Small residues are, of course, always nonaromatic for naturally
10 occurring protein amino acids. .

For the naturally occurring protein amino acids, subclassification according to the foregoing scheme is as follows.

Acidic: Aspartic acid and Glutamic acid;

Basic/noncyclic: Arginine, Lysine;

15 Basic/cyclic: Histidine;

Neutral/small: Glycine, Serine, Cysteine, Alanine;

Neutral/polar/large/nonaromatic: Threonine, Asparagine, Glutamine;

Neutral/polar/large/aromatic: Tyrosine;

Neutral/nonpolar/large/nonaromatic: Valine, Isoleucine, Leucine, Methionine;

20 Neutral/nonpolar/large/aromatic: Phenylalanine, and Tryptophan.

The gene-encoded secondary amino acid proline, although technically within the group neutral/nonpolar/large/ cyclic and nonaromatic, is a special case due to its known effects on the secondary conformation of peptide chains, and is not, therefore, included in this defined group.

25 Certain commonly encountered amino acids, which are not encoded by the genetic code, include, for example, beta-alanine (b-Ala), or other omega-amino acids, such as 2,3-diamino propionic (2,3-Dap), 2,4-diaminobutyric (2,4-Dab), 4-amino butyric (g-Abu) and so forth, alpha-aminoisobutyric acid (Aib), sarcosine (Sar), ornithine (Orn), citrulline (Cit), homoarginine (Har), homolysine (homoLys), n-butylamidinoglycine (Bag), 4-guanidinophenylalanine (4-Gpa), 3-guanidinophenylalanine (3-Gpa), 4-amidinophenylalanine (4-Apa), 3-amidinophenylalanine (3-Apa), 4-aminocyclohexylglycine (4-Acg), 4-aminophenylalanine (4-NH₂-Phe), 3-aminophenylalanine (3-NH₂-Phe), 3-(3-pyridyl)-Ala (3-Py-Ala), 3-(3-piperdanyl)-Ala (3-Pip-Ala), 3-(3-Me-3-pyridyl)-Ala (3-Me-3-Py-Ala), 3-(4-pyridyl)-Ala (4-Py-Ala), 3-(4-piperdanyl)-Ala (4-Pip-Ala), 3-(3-amidino-3-piperdanyl)-Ala (3-Amidino-3-Pip-Ala), 3-(4-amidino-4-piperdanyl)-Ala (4-Amidino-4-Pip-Ala), 4-aminomethylphenylalanine (4H₂NCH₂-Phe), and 4-aminomethylphenylglycine (4H₂NCH₂-Phg). These also fall conveniently into particular categories.

5 Based on the above definitions:
Sar, b-Ala, g-Abu, and Aib are neutral/small;
Orn, Har, homoLys, Bag, 2,3-Dap, 2,4-Dab, 4-Gpa, 3-Gpa, 4-Apa, 3-Apa, 4-
Acg, 4-NH₂-Phe, 3-NH₂-Phe are basic;
Cit, is neutral/polar/ large/nonaromatic; and

10 The various omega-amino acids are classified according to size as
neutral/nonpolar/small (b-Ala, i.e., 3-aminopropionic, 4-aminobutyric) or large (all
others).

15 Amino acid substitutions for those indicated in the structure/formula provided
can be included in peptide compounds within the scope of the invention and can be
classified within this general scheme according to their structure.

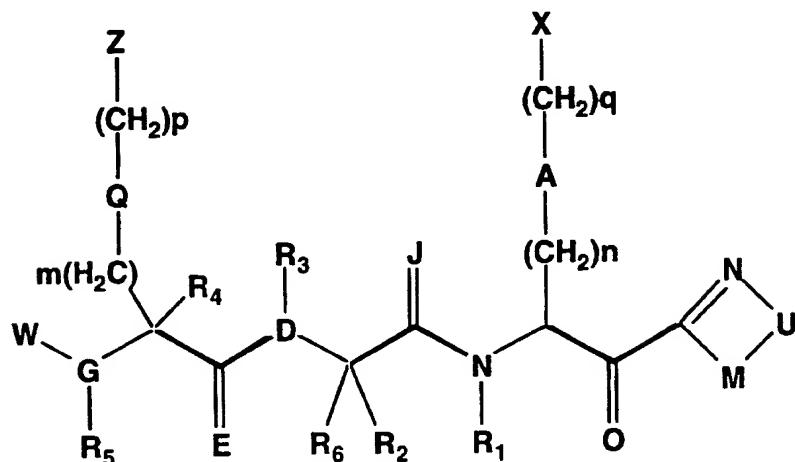
In all of the peptides of the invention, one or more amide linkages (-CO-NH-) may optionally be replaced with another linkage which is an isostere such as -CH₂NH-, -CH₂S-, -CH₂CH₂, -CH=CH- (cis and trans), -COCH₂-, -CH(OH)CH₂- and -CH₂SO-. This replacement can be made by methods known in the art. The

20 following references describe preparation of peptide analogs which include these alternative-linking moieties: Spatola, A.F., Vega Data (March 1983), Vol. 1, Issue 3, "Peptide Backbone Modifications" (general review); Spatola, A.F., in "Chemistry and Biochemistry of Amino Acids, Peptides and Proteins," B. Weinstein, eds., Marcel Dekker, New York, p. 267 (1983) (general review); Morley, J.S., Trends Pharm Sci 25 (1980) pp. 463-468 (general review); Hudson, D., *et al.*, Int J Pept Prot Res (1979) 14:177-185 (-CH₂NH-, -CH₂CH₂-); Spatola, A.F., *et al.*, Life Sci (1986) 38:1243-1249 (-CH₂-S); Hann, M.M., J Chem Soc Perkin Trans I (1982) 307-314 (-CH=CH-, cis and trans); Almquist, R.G., *et al.*, J Med Chem (1980) 23:1392-1398 (-COCH₂-); Jennings-White, C., *et al.*, Tetrahedron Lett (1982) 23:2533 (-COCH₂-); Szelke, M., 30 *et al.*, European Application EP 45665; CA:97:39405 (1982) (-CH(OH)CH₂-); Holladay, M.W., *et al.*, Tetrahedron Lett (1983) 24:4401-4404 (-C(OH)CH₂-); and Hruby, V.J., Life Sci (1982) 31:189-199 (-CH₂-S-).

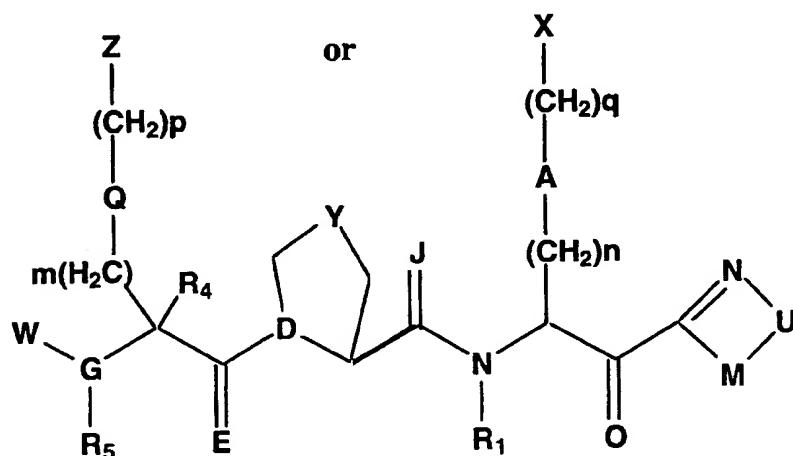
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Preferred Embodiments

In preferred embodiments, the present invention provides compounds of the formula:



10



wherein:

m = 0,1,2,3,4;

n = 0,1,2,3,4;

p = 0,1,2,3,4;

q = 0,1,2,3,4;

Y = NH, S, O, CH₂, CH-OH, CH₂CH₂, C=O;A = piperdiny1, pyrrolidiny1, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, C₃-6heteroaryl, or is absent;

15

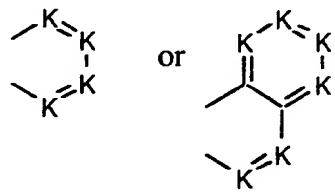
R₁ = H or C₁₋₃alkyl;J = O or H₂;

5 R₂ = H or C₁₋₃alkyl;
 D = N, CH, NCH₂, NCH₂CH₂, CHCH₂;
 R₃ = H or C₁₋₃alkyl;
 E = O or H₂;
 R₄ = H or CH₃;

10 M = NH, N-CH₃, O, S, SO, SO₂ or CH₂;
 Q = piperidinyl, pyrrolidinyl, C₃₋₈ cycloalkyl, phenyl, substituted
 phenyl, naphthyl, pyridyl, or is absent;
 G = N, CH, or is H;
 R₅ = H or C₁₋₃ alkyl or is absent if G is H;

15 R₆ = H or CH₃;
 U = is selected from a group consisting of

where n = 0-4; R₇ and R₈ are independently selected from a group consisting of H, C₁₋₁₀alkyl, aryl, arylalkyl, halogen, nitro, an amino group of formula -NR₉R₁₀, an acylamino group of formula -NHCOR₁₁, hydroxy, an acyloxy group of formula -OCOR₁₂, C₁₋₄alkyloxy, C₁₋₄alkyl, trifluoromethyl, carboxy, cyano, phenyl, aromatic heterocyclic group as defined herein below, C₁₋₄alkyloxycarbonyl, an aminocarbonyl group of formula CONR₁₃R₁₄, sulfo, sulfonamido of formula SO₂NR₁₅R₁₆ and C₁₋₆ hydroxyalkyl; wherein R₉, R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆ are the same or different and = H, C₁₋₆ alkyl, C₁₋₃arylalkyl or aryl; and if M is absent:



30 K = C or N;

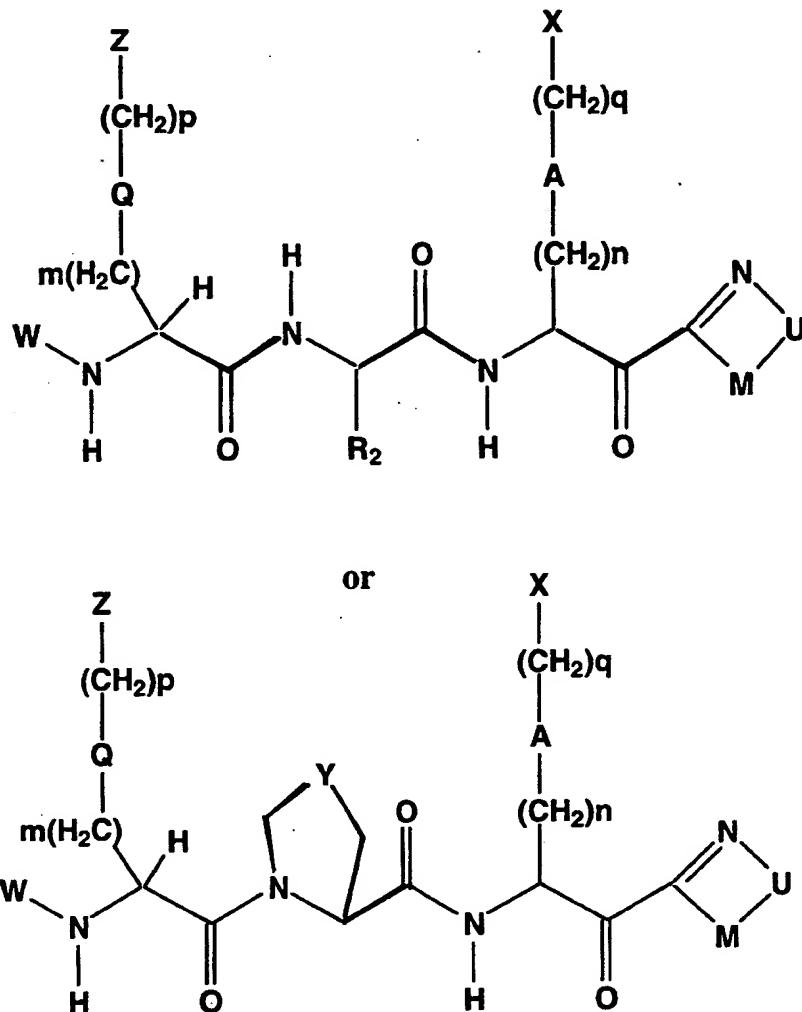
5 W = H, arylacyl, heteroarylacyl, arylC₁₋₃alkylsulfonyl, arylsulfonyl,
 substituted arylsulfonyl, arylC₁₋₄alkenylsulfonyl, C₁₋₈
 alkylsulfonyl, heteroarylC₁₋₃alkylsulfonyl, heteroarylsulfonyl,
 aryloxycarbonyl, C₁₋₆alkyloxycarbonyl, arylC₁₋
 3alkyloxycarbonyl, arylaminocarbonyl, C₁₋
10 6alkylaminocarbonyl, arylC₁₋₃alkylaminocarbonyl, HOOC-C₀₋
 3alkylcarbonyl, or is absent if G is H;

X = H, C₁₋₃alkyl, NR'R'', NH-C(NR'R'')=NH, NH-C(NHR')=NR'', NH-
 C(R')=NR'', S-C(NR'R'')=NH, S-C(NHR')=NR'', C(NR'R'')=NH,
 C(NHR')=NR'' or CR'=NR''; where: R',R'' are the same or
15 different and = H, C₁₋₆alkyl, C₁₋₃arylalkyl, aryl or where R'R''
 forms a cyclic ring containing (CH₂)_p where p=2-5, with the
 proviso that when X is H or C₁₋₃alkyl, then A must contain at
 least one N atom;

Z = H, C₁₋₃alkyl, NR'R'', NH-C(NR'R'')=NH, NH-C(NHR')=NR'', NH-
20 C(R')=NR'', S-C(NR'R'')=NH, S-C(NHR')=NR'', C(NR'R'')=NH,
 C(NHR')=NR'' or CR'=NR''; where: R',R'' are the same or
 different and = H, C₁₋₆alkyl, C₁₋₃arylalkyl, aryl or where R'R''
 forms a cyclic ring containing (CH₂)_p where p=2-5, with the
 proviso that when Z is H or C₁₋₃alkyl, then Q must contain at
25 least one N atom;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

Some preferred compounds of the present invention include those of formula:



5 wherein:

m = 0,1,2,3,4;

n = 0,1,2,3,4;

p = 0,1,2,3,4;

10 q = 0,1,2,3,4;

Y = NH, S, O, CH₂, CH-OH, CH₂CH₂;

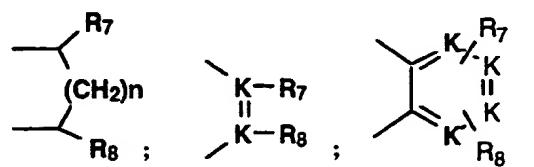
A = piperdinyl, pyrrolidinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, C₃₋₆heteroaryl, or is absent;

M = NH, N-CH₃, O, S, SO, SO₂ or CH₂;

15 Q = piperdinyl, pyrrolidinyl, C₃₋₈ cycloalkyl, phenyl, substituted phenyl, naphthyl, pyridyl, or is absent;

U = is selected from a group consisting of

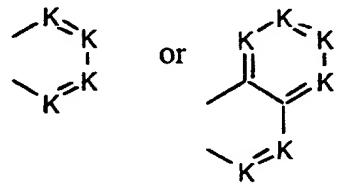
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10

where $n = 0-4$; R_7 and R_8 are independently selected from a group consisting of H, C₁₋₁₀alkyl, aryl, arylalkyl, halogen, nitro, an amino group of formula -NR₉R₁₀, an acylamino group of formula -NHCOR₁₁, hydroxy, an acyloxy group of formula -OCOR₁₂, C₁₋₄alkyloxy, C₁₋₄alkyl, trifluoromethyl, carboxy, cyano, phenyl, aromatic heterocyclic group as defined herein below, C₁₋₄alkyloxycarbonyl, an aminocarbonyl group of formula CONR₁₃R₁₄, sulfo, sulfonamido of formula SO₂NR₁₅R₁₆ and C₁₋₆ hydroxyalkyl; wherein R₉, R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆ are the same or different and = H, C₁₋₆ alkyl, C₁₋₃arylalkyl or aryl; and if M is absent:

15



K = C or N;

20

W = H, arylacyl, heteroarylacyl, arylC₁₋₃alkylsulfonyl, arylsulfonyl, substituted arylsulfonyl, arylC₁₋₄alkenylsulfonyl, C₁₋₈alkylsulfonyl, heteroarylC₁₋₃alkylsulfonyl, heteroarylalkylsulfonyl, aryloxycarbonyl, C₁₋₆ alkyloxycarbonyl, arylC₁₋₃alkyloxycarbonyl, arylaminocarbonyl, C₁₋₆alkylaminocarbonyl, arylC₁₋₃alkylaminocarbonyl, HOOC-C₀₋₃alkylcarbonyl, or is absent if G is H;

25

X = H, C₁₋₃alkyl, NR'R'', NH-C(NR'R'')=NH, NH-C(NHR')=NR'', NH-C(R')=NR'', S-C(NR'R'')=NH, S-C(NHR')=NR'', C(NR'R'')=NH, C(NHR')=NR'' or CR'=NR''; where: R', R'' are the same or different and = H, C₁₋₆alkyl, C₁₋₃arylalkyl, aryl or where R'R'' forms a cyclic ring containing (CH₂)_p where p=2-5, with the

30

5 proviso that when X is H or C₁₋₃alkyl, then A must contain at least one N atom

Z = H, C₁₋₃alkyl, NR'R'', NH-C(NR'R'')=NH, NH-C(NHR')=NR'', NH-C(R')=NR'', S-C(NR'R'')=NH, S-C(NHR')=NR'', C(NR'R'')=NH, C(NHR')=NR'' or CR'=NR''; where: R', R'' are the same or

10 different and = H, C₁₋₆alkyl, C₁₋₃arylalkyl, aryl or where R'R'' forms a cyclic ring containing (CH₂)_p where p=2-5, with the proviso that when Z is H or C₁₋₃alkyl, then Q must contain at least one N atom;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug

15 derivatives thereof.

A preferred substituent Y is S, O, CH₂, CH₂CH₂.

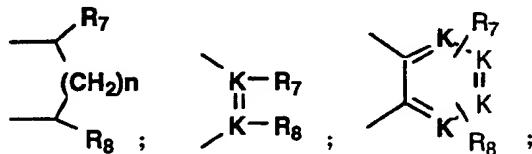
A preferred substituent A is piperdanyl, pyrrolidinyl, cyclopentyl, cyclohexyl, phenyl, C₃₋₆heteroaryl, or is absent.

A preferred substituent D is N, CH, NCH₂.

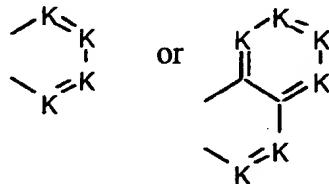
20 A preferred substituent M is NH, O, S, CH₂ or is absent.

A preferred substituent Q is piperdanyl, pyrrolidinyl, C₃₋₈ cycloalkyl, phenyl, substituted phenyl, or is absent.

A preferred substituent U is selected from



25 where n = 0-2; R₇ and R₈ are independently selected from a group consisting of H, C₁₋₁₀alkyl, aryl, arylalkyl, halogen, nitro, trifluoromethyl, carboxy, or cyano; and if M is absent:



A preferred substituent K is C or N.

30 A preferred substituent W is arylC₁₋₃alkylsulfonyl, arylsulfonyl, substituted arylsulfonyl, arylC₁₋₄alkenylsulfonyl, C₁₋₈ alkylsulfonyl, heteroarylC₁₋₃alkylsulfonyl, heteroarylsulfonyl, C₁₋₆ alkyloxycarbonyl, arylC₁₋₃alkyloxycarbonyl.

5 A preferred substituent X is NR'R'', NH-C(NR'R'')=NH, NH-C(NHR')=NR'',
 NH-C(R')=NR'', S-C(NR'R'')=NH, S-C(NHR')=NR'', C(NR'R'')=NH, C(NHR')=NR'';
 where: R',R'' are the same or different and = H, C₁₋₆alkyl.

A preferred substituent Z is , NH-C(NR'R'')=NH, NH-C(NHR')=NR'', NH-C(R')=NR'', S-C(NR'R'')=NH, S-C(NHR')=NR'', C(NR'R'')=NH, C(NHR')=NR''; where:
 10 R',R'' are the same or different and = H, C₁₋₆alkyl.

Preferred compounds as a whole may be selected from any combination of the formulas presented in this specification with one or more of the preferred groupings of substituents at a particular location.

Some preferred embodiments of the invention are shown in the following
 15 Table 1.

TABLE 1

		Inhibitory Activity (IC ₅₀) μM		
	<u>STRUCTURE</u>	<u>Factor Xa</u>	<u>Prothrombinase</u>	<u>Thrombin</u>
20	H-D-Arg-Gly-Arg-thiazole	0.011	0.010	41
	BnSO ₂ -(D)-Arg-Gly-Arg-thiazole	0.00065	0.00045	10
Other preferred compounds of the present invention are shown but not limited to the following list of compounds which have the general structure:				
	W - (Basic amino acid) - (Neutral/small amino acid) - (Arg or Basic amino acid)-			
25	Heterocycle			
	PhCH ₂ CH ₂ -SO ₂ -(D)-Arg-Gly-Arg-Thiazole			
	C ₆ H ₁₁ CH ₂ CH ₂ SO ₂ -(D)-Arg-Gly-Arg-Thiazole			
	Me ₂ C-C ₆ H ₄ SO ₂ -(D)-Arg-Gly-Arg-Thiazole			
	C ₁₀ H ₇ SO ₂ -(D)-Arg-Gly-Arg-Thiazole			
30	Me ₃ SiCH ₂ CH ₂ CH ₂ SO ₂ -(D)-Arg-Gly-Arg-Thiazole			
	BnSO ₂ -(D)-4-Apa-Gly-Arg-Thiazole			
	BnSO ₂ -(D)-4-Gpa-Gly-Arg-Thiazole			
	BnSO ₂ -(D)-Acp-Gly-Arg-Thiazole			
	BnSO ₂ -(D)-homo-Lys-Gly-Arg-Thiazole			
35	BnSO ₂ -(D)-Arg-Sar-Arg-Thiazole			
	BnSO ₂ -(D)-Arg-Pro-Arg-Thiazole			
	BnSO ₂ -(D)-Arg-Gly-4-Acp-Thiazole			

5 BnSO₂-(D)-Arg-Gly-(3-NH₂-Phe)-Thiazole
 BnSO₂-(D)-Arg-Gly-(4-NH₂-Phe)-Thiazole
 BnSO₂-(D)-Arg-Gly-Gpa-Thiazole
 Boc-D-(2,3-Dap)-Gly-Arg-Thiazole
 Boc-D-(2,4-Dab)-Gly-Arg-Thiazole
10 g-Abu-Gly-Arg-Thiazole
 Boc-D-Orn-Gly-Arg-Thiazole
 Boc-D-homoLys-Gly-Arg-Thiazole
 Boc-Bag-Gly-Arg-Thiazole
 Boc-D-4-Gpa-Gly-Arg-Thiazole
15 Boc-D-3-Gpa-Gly-Arg-Thiazole
 Boc-D-4-Apa-Gly-Arg-Thiazole
 Boc-D-3-Apa-Gly-Arg-Thiazole
 Boc-D-4-Acg-Gly-Arg-Thiazole
 Boc-D-(4-NH₂Phe)-Gly-Arg-Thiazole
20 Boc-D-(3-NH₂Phe)-Gly-Arg-Thiazole
 BnSO₂-D-(2,3-Dap)-Gly-Arg-Thiazole
 BnSO₂-D-(2,4-Dab)-Gly-Arg-Thiazole
 BnSO₂-D-Orn-Gly-Arg-Thiazole
 BnSO₂-Bag-Gly-Arg-Thiazole
25 BnSO₂-D-3-Gpa-Gly-Arg-Thiazole
 BnSO₂-D-3-Apa-Gly-Arg-Thiazole
 BnSO₂-D-(4-NH₂Phe)-Gly-Arg-Thiazole
 BnSO₂-D-(3-NH₂Phe)-Gly-Arg-Thiazole
 BnSO₂-D-(2,3-Dap)-Gly-Arg-Benzothiazole
30 BnSO₂-D-(2,4-Dab)-Gly-Arg-Benzothiazole
 BnSO₂-D-Orn-Gly-Arg-Benzothiazole
 BnSO₂-Bag-Gly-Arg-Benzothiazole
 BnSO₂-D-4-Gpa-Gly-Arg-Benzothiazole
 BnSO₂-D-3-Gpa-Gly-Arg-Benzothiazole
35 BnSO₂-D-4-Apa-Gly-Arg-Benzothiazole
 BnSO₂-D-3-Apa-Gly-Arg-Benzothiazole
 BnSO₂-D-4-Acg-Gly-Arg-Benzothiazole

5 BnSO₂-D-(4-NH₂Phe)-Gly-Arg-Benzothiazole
 BnSO₂-D-(3-NH₂Phe)-Gly-Arg-Benzothiazole
 BnSO₂-D-Arg-Gly-(2,4-Dab)-Benzothiazole
 BnSO₂-D-Arg-Gly-(homoLys)-Benzothiazole
 BnSO₂-D-Arg-Gly-(4-Gpa)-Benzothiazole
10 BnSO₂-D-Arg-Gly-(3-Gpa)-Benzothiazole
 BnSO₂-D-Arg-Gly-(4-Apa)-Benzothiazole
 BnSO₂-D-Arg-Gly-(3-Apa)-Benzothiazole
 BnSO₂-D-Arg-Gly-(4-NH₂Phe)-Benzothiazole
 BnSO₂-D-Arg-Gly-(3-NH₂Phe)-Benzothiazole
15 Me₃SiCH₂CH₂CH₂SO₂-(D)-Arg-Gly-Arg-Benzothiazole
 BnSO₂-(D)-homo-Lys-Gly-Arg-Benzothiazole
 BnSO₂-(D)-homo-Lys-Gly-Arg-Benzoxazole
 PhCH₂CH₂SO₂-(D)-Arg-Gly-Arg-Benzothiazole
 BnSO₂-(D)-Arg-Sar-Arg-Benzothiazole
20 BnSO₂-(D)-Arg-Pro-Arg-Benzothiazole
 BnSO₂-(D)-Arg-Gly-Acg-Benzothiazole
 BnSO₂-(D)-Arg-Gly-Arg-Benzothiazole
 PhCH₂CH₂SO₂-(D)-Arg-Gly-4-Acg-Benzothiazole
 BnSO₂-(D)-Arg-Gly-Arg-Oxazole
25 Boc-D-(2,3-Dap)-Gly-Arg-Oxazole
 Boc-D-(2,4-Dab)-Gly-Arg-Oxazole
 g-Abu-Gly-Arg-Oxazole
 Boc-D-Orn-Gly-Arg-Oxazole
 Boc-D-homoLys-Gly-Arg-Oxazole
30 Boc-Bag-Gly-Arg-Oxazole
 Boc-D-4-Gpa-Gly-Arg-Oxazole
 Boc-D-3-Gpa-Gly-Arg-Oxazole
 Boc-D-4-Apa-Gly-Arg-Oxazole
 Boc-D-3-Apa-Gly-Arg-Oxazole
35 Boc-D-4-Acg-Gly-Arg-Oxazole
 Boc-D-(4-NH₂Phe)-Gly-Arg-Oxazole
 Boc-D-(3-NH₂Phe)-Gly-Arg-Oxazole

5 BnSO₂-D-(2,3-Dap)-Gly-Arg-Oxazole
 BnSO₂-D-(2,4-Dab)-Gly-Arg-Oxazole
 BnSO₂-D-Orn-Gly-Arg-Oxazole
 BnSO₂-Bag-Gly-Arg-Oxazole
 BnSO₂-D-3-Gpa-Gly-Arg-Oxazole

10 BnSO₂-D-3-Apa-Gly-Arg-Oxazole
 BnSO₂-D-(4-NH₂Phe)-Gly-Arg-Oxazole
 BnSO₂-D-(3-NH₂Phe)-Gly-Arg-Oxazole
 BnSO₂-D-(2,3-Dap)-Gly-Arg-Oxazole
 BnSO₂-D-(2,4-Dab)-Gly-Arg-Oxazole

15 BnSO₂-D-Orn-Gly-Arg-Oxazole
 BnSO₂-Bag-Gly-Arg-Oxazole
 BnSO₂-D-4-Gpa-Gly-Arg-Oxazole
 BnSO₂-D-3-Gpa-Gly-Arg-Oxazole
 BnSO₂-D-4-Apa-Gly-Arg-Oxazole

20 BnSO₂-D-3-Apa-Gly-Arg-Oxazole
 BnSO₂-D-4-Acg-Gly-Arg-Oxazole
 BnSO₂-D-(4-NH₂Phe)-Gly-Arg-Oxazole
 BnSO₂-D-(3-NH₂Phe)-Gly-Arg-Oxazole
 BnSO₂-D-Arg-Gly-(2,4-Dab)-Oxazole

25 BnSO₂-D-Arg-Gly-(homoLys)-Oxazole
 BnSO₂-D-Arg-Gly-(4-Gpa)-Oxazole
 BnSO₂-D-Arg-Gly-(3-Gpa)-Oxazole
 BnSO₂-D-Arg-Gly-(4-Apa)-Oxazole
 BnSO₂-D-Arg-Gly-(3-Apa)-Oxazole

30 BnSO₂-D-Arg-Gly-(4-NH₂Phe)-Oxazole
 BnSO₂-D-Arg-Gly-(3-NH₂Phe)-Oxazole
 BnSO₂-D-(2,3-Dap)-Gly-Arg-Benzoxazole
 BnSO₂-D-(2,4-Dab)-Gly-Arg-Benzoxazole
 BnSO₂-D-Orn-Gly-Arg-Benzoxazole

35 BnSO₂-Bag-Gly-Arg-Benzoxazole
 BnSO₂-D-4-Gpa-Gly-Arg-Benzoxazole

5 BnSO₂-D-3-Gpa-Gly-Arg-Benzoxazole
 BnSO₂-D-4-Apa-Gly-Arg-Benzoxazole
 BnSO₂-D-3-Apa-Gly-Arg-Benzoxazole
 BnSO₂-D-4-Acg-Gly-Arg-Benzoxazole
 BnSO₂-D-(4-NH₂Phe)-Gly-Arg-Benzoxazole

10 BnSO₂-D-(3-NH₂Phe)-Gly-Arg-Benzoxazole
 BnSO₂-D-Arg-Gly-(2,4-Dab)-Benzoxazole
 BnSO₂-D-Arg-Gly-(homoLys)-Benzoxazole
 BnSO₂-D-Arg-Gly-(4-Gpa)-Benzoxazole
 BnSO₂-D-Arg-Gly-(3-Gpa)-Benzoxazole

15 BnSO₂-D-Arg-Gly-(4-Apa)-Benzoxazole
 BnSO₂-D-Arg-Gly-(3-Apa)-Benzoxazole
 BnSO₂-D-Arg-Gly-(4-NH₂Phe)-Benzoxazole
 BnSO₂-D-Arg-Gly-(3-NH₂Phe)-Benzoxazole
 Me₃SiCH₂CH₂CH₂SO₂-(D)-Arg-Gly-Arg-Benzoxazole

20 BnSO₂-(D)-homo-Lys-Gly-Arg-Benzoxazole
 BnSO₂-(D)-homo-Lys-Gly-Arg-Benzoxazole
 PhCH₂CH₂SO₂-(D)-Arg-Gly-Arg-Benzoxazole
 BnSO₂-(D)-Arg-Sar-Arg-Benzoxazole
 BnSO₂-(D)-Arg-Pro-Arg-Benzoxazole

25 BnSO₂-(D)-Arg-Gly-Acg-Benzoxazole
 BnSO₂-(D)-Arg-Gly-Arg-Benzoxazole
 PhCH₂CH₂SO₂-(D)-Arg-Gly-4-Acg-Benzoxazole
 BnSO₂-(D)-Arg-Gly-Arg-Benzoxazole
 BnSO₂-(D)-Arg-Gly-Acg-Benzoxazole

30 PhCH₂CH₂SO₂-(D)-Arg-Gly-Arg-Benzoxazole
 PhCH₂CH₂SO₂-(D)-Arg-Gly-4-Acg-Benzoxazole
 Me₃SiCH₂CH₂CH₂SO₂-(D)-Arg-Gly-Arg-Benzoxazole
 BnSO₂-(D)-Arg-Gly-Arg-Oxazoline
 Boc-D-(2,3-Dap)-Gly-Arg-Oxazoline

35 Boc-D-(2,4-Dab)-Gly-Arg-Oxazoline
 g-Abu-Gly-Arg-Oxazoline

5 Boc-D-Orn-Gly-Arg-Oxazoline
 Boc-D-homoLys-Gly-Arg-Oxazoline
 Boc-Bag-Gly-Arg-Oxazoline
 Boc-D-4-Gpa-Gly-Arg-Oxazoline
 Boc-D-3-Gpa-Gly-Arg-Oxazoline
10 Boc-D-4-Apa-Gly-Arg-Oxazoline
 Boc-D-3-Apa-Gly-Arg-Oxazoline
 Boc-D-4-Acg-Gly-Arg-Oxazoline
 Boc-D-(4-NH₂Phe)-Gly-Arg-Oxazoline
 Boc-D-(3-NH₂Phe)-Gly-Arg-Oxazoline
15 BnSO₂-D-(2,3-Dap)-Gly-Arg-Oxazoline
 BnSO₂-D-(2,4-Dab)-Gly-Arg-Oxazoline
 BnSO₂-D-Orn-Gly-Arg-Oxazoline
 BnSO₂-Bag-Gly-Arg-Oxazoline
 BnSO₂-D-3-Gpa-Gly-Arg-Oxazoline
20 BnSO₂-D-3-Apa-Gly-Arg-Oxazoline
 BnSO₂-D-(4-NH₂Phe)-Gly-Arg-Oxazoline
 BnSO₂-D-(3-NH₂Phe)-Gly-Arg-Oxazoline
 BnSO₂-D-(2,3-Dap)-Gly-Arg-Oxazoline
 BnSO₂-D-(2,4-Dab)-Gly-Arg-Oxazoline
25 BnSO₂-D-Orn-Gly-Arg-Oxazoline
 BnSO₂-Bag-Gly-Arg-Oxazoline
 BnSO₂-D-4-Gpa-Gly-Arg-Oxazoline
 BnSO₂-D-3-Gpa-Gly-Arg-Oxazoline
 BnSO₂-D-4-Apa-Gly-Arg-Oxazoline
30 BnSO₂-D-3-Apa-Gly-Arg-Oxazoline
 BnSO₂-D-4-Acg-Gly-Arg-Oxazoline
 BnSO₂-D-(4-NH₂Phe)-Gly-Arg-Oxazoline
 BnSO₂-D-(3-NH₂Phe)-Gly-Arg-Oxazoline
 BnSO₂-D-Arg-Gly-(2,4-Dab)-Oxazoline
35 BnSO₂-D-Arg-Gly-(homoLys)-Oxazoline
 BnSO₂-D-Arg-Gly-(4-Gpa)-Oxazoline

5 BnSO₂-D-Arg-Gly-(3-Gpa)-Oxazoline
 BnSO₂-D-Arg-Gly-(4-Apa)-Oxazoline
 BnSO₂-D-Arg-Gly-(3-Apa)-Oxazoline
 BnSO₂-D-Arg-Gly-(4-NH₂Phe)-Oxazoline
 BnSO₂-D-Arg-Gly-(3-NH₂Phe)-Oxazoline

10 BnSO₂-(D)-Arg-Gly-Arg-Imidazole
 BnSO₂-(D)-Arg-Gly-Arg-Pyridine
 BnSO₂-(D)-Arg-Gly-Arg-2-(1-methyl-tetrazole)
 BnSO₂-(D)-Arg-Gly-Arg-2-(4-methyl-tetrazole)
 MeSO₂-(D)-Arg-Gly-Arg-Thiazole

15 BnSO₂-(D)-(4-H₂NCH₂-Phe)-Gly-Arg-Thiazole
 BnSO₂-(D)-(4-H₂NCH₂-Phg)-Gly-Arg-Thiazole
 BnSO₂-(D)-(3-Py-Ala)-Gly-Arg-Thiazole
 BnSO₂-(D)-(3-Me-3-Py-Ala)-Gly-Arg-Thiazole
 BnSO₂-(D)-(3-Pip-Ala)-Gly-Arg-Thiazole

20 BnSO₂-(D)-(4-Pip-Ala)-Gly-Arg-Thiazole
 BnSO₂-(D)-(3-Amidino-3-Pip-Ala)-Gly-Arg-Thiazole

25 This invention also encompasses prodrug derivatives of the compounds contained herein. The term "prodrug" refers to a pharmacologically inactive derivative of a parent drug molecule that requires biotransformation, either spontaneous or enzymatic, within the organism to release the active drug. Prodrugs are variations or derivatives of the compounds of this invention which have metabolically cleavable groups and become, by solvolysis under physiological conditions, or by enzymatic degradation the compounds of the invention which are pharmaceutically active *in vivo*. Prodrug compounds of this invention may be called

30 single, double, triple etc., depending on the number of biotransformation steps required to release the active drug within the organism, and indicating the number of functionalities present in a precursor-type form. Prodrug forms often offer advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (see, Bundgard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier,

35 Amsterdam 1985 and Silverman, R.B., The Organic Chemistry of Drug Design and Drug Action, pp. 352-401, Academic Press, San Diego, CA, 1992). Prodrugs commonly known in the art include acid derivatives well known to practitioners of the

5 art, such as, for example, esters prepared by reaction of the parent acids with a suitable alcohol, or amides prepared by reaction of the parent acid compound with an amine, or basic groups reacted to form an acylated base derivative. Moreover, the prodrug derivatives of this invention may be combined with other features herein taught to enhance bioavailability.

10

Preparation of Compounds

The compounds of the present invention may be synthesized by either solid or liquid phase methods described and referenced in standard textbooks, or by a combination of both methods. These methods are well known in the art. See, 15 Bodanszky, M., in "The Principles of Peptide Synthesis", Hafner, K., Rees, C.W., Trost, B.M., Lehn, J.-M., Schleyer, P. v-R., Zahradnik, R., Eds., Springer-Verlag, Berlin, 1984. Starting materials are commercially available reagents and reactions are carried out in standard laboratory glassware and reaction vessels under reaction conditions of standard temperature and pressure, except where otherwise indicated.

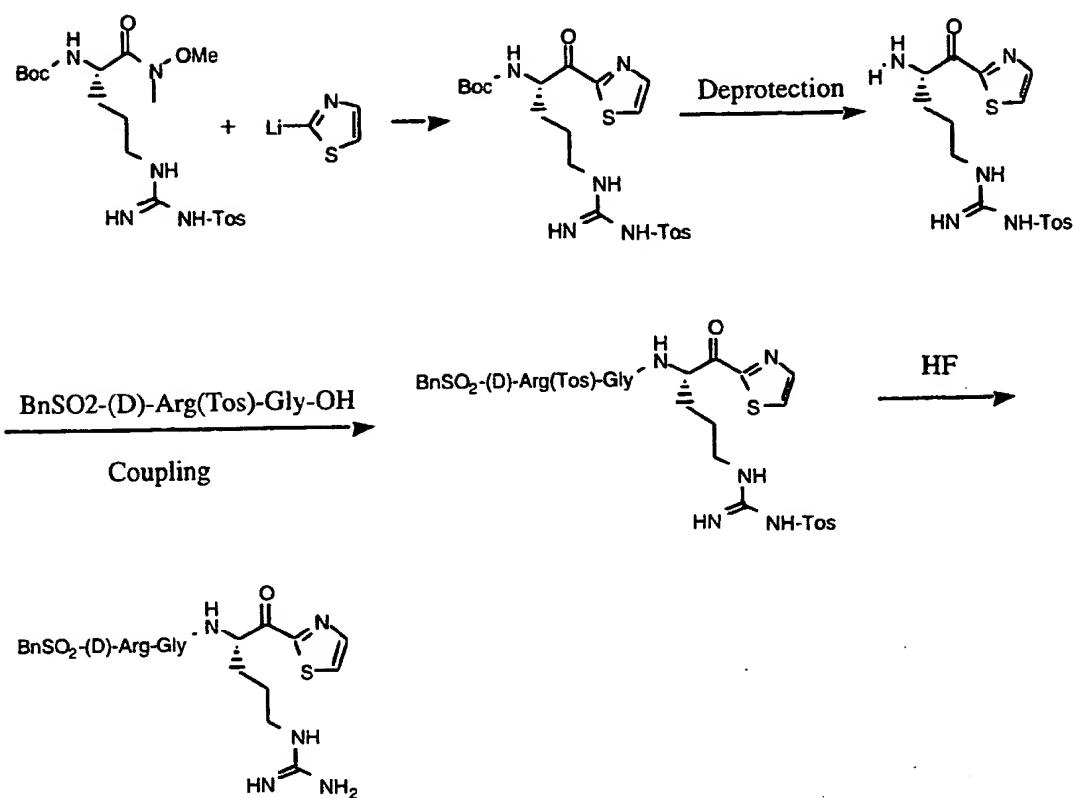
20 The ketoheterocyclic compounds of the invention can be prepared by methods described by Dondoni, A. et. al., *Synthesis*, 1162-1176 (1993); Edwards, P.D., et. al., *J. Amer. Chem. Soc.*, 114, 1854-1863 (1992); Tsutsumi, S., et. al., *J. Med. Chem.* 37, 3492-3502 (1994); and Edwards, P.D., et. al., *J. Med. Chem.* 38, 76-85 (1995).

25 The starting materials used in any of these methods are commercially available from chemical vendors such as Aldrich, Sigma, Nova Biochemicals, Bachem Biosciences, and the like, or may be readily synthesized by known procedures.

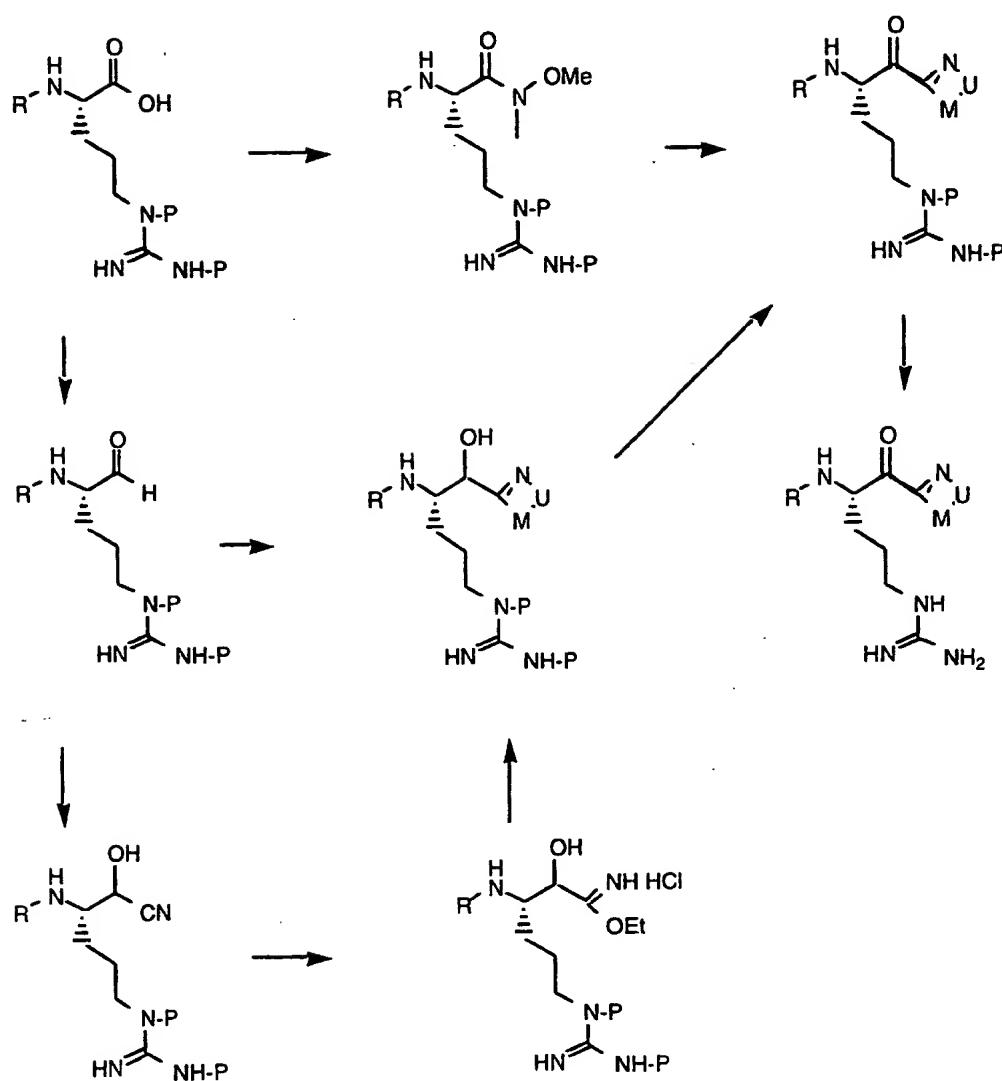
30 During the synthesis of these compounds, the functional groups of the amino acid derivatives used in these methods are protected by blocking groups to prevent cross reaction during the coupling procedure. Examples of suitable blocking groups and their use are described in "The Peptides: Analysis, Synthesis, Biology", Academic Press, Vol. 3 (Gross, E. & Meienhofer, J., Eds., 1981) and Vol. 9 (, S. &, Eds., 1987), the disclosures of which are incorporated herein by reference.

35 Two exemplary synthesis schemes are outlined directly below, and the specific syntheses are described in the Examples. The reaction products are isolated and purified by conventional methods, typically by solvent extraction into a compatible solvent. The products may be further purified by column chromatography or other appropriate methods.

5

Scheme 1

5

Scheme 2

P = Protecting group; R = Protecting group, protected or substituted amino acid, or
 10 protected or substituted dipeptide unit.

Compositions and Formulations

The compounds of this invention may be isolated as the free acid or base or converted to salts of various inorganic and organic acids and bases. Such salts are within the scope of this invention. Non-toxic and physiologically compatible salts are particularly useful although other less desirable salts may have use in the processes of isolation and purification.

5 A number of methods are useful for the preparation of the salts described above and are known to those skilled in the art. For example, reaction of the free acid or free base form of a compound of the structures recited above with one or more molar equivalents of the desired acid or base in a solvent or solvent mixture in which the salt is insoluble, or in a solvent like water after which the solvent is
10 removed by evaporation, distillation or freeze drying. Alternatively, the free acid or base form of the product may be passed over an ion exchange resin to form the desired salt or one salt form of the product may be converted to another using the same general process.

Diagnostic applications of the compounds of this invention will typically utilize
15 formulations such as solution or suspension. In the management of thrombotic disorders the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for oral administration, suppositories, sterile solutions or suspensions or injectable administration, and the like, or incorporated into shaped articles. Subjects in need of treatment (typically mammalian) using the compounds
20 of this invention can be administered dosages that will provide optimal efficacy. The dose and method of administration will vary from subject to subject and be dependent upon such factors as the type of mammal being treated, its sex, weight, diet, concurrent medication, overall clinical condition, the particular compounds employed, the specific use for which these compounds are employed, and other
25 factors which those skilled in the medical arts will recognize.

Formulations of the compounds of this invention are prepared for storage or administration by mixing the compound having a desired degree of purity with physiologically acceptable carriers, excipients, stabilizers etc., and may be provided in sustained release or timed release formulations. Acceptable carriers or diluents
30 for therapeutic use are well known in the pharmaceutical field, and are described, for example, in *Remington's Pharmaceutical Sciences*, Mack Publishing Co., (A.R. Gennaro edit. 1985). Such materials are nontoxic to the recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, acetate and other organic acid salts, antioxidants such as ascorbic acid, low
35 molecular weight (less than about ten residues) peptides such as polyarginine, proteins, such as serum albumin, gelatin, or immunoglobulins, hydrophilic polymers such as polyvinylpyrrolidinone, amino acids such as glycine, glutamic acid, aspartic acid, or arginine, monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose or dextrans, chelating agents

5 such as EDTA, sugar alcohols such as mannitol or sorbitol, counterions such as sodium and/or nonionic surfactants such as Tween, Pluronics or polyethylen glycol.

Dosage formulations of the compounds of this invention to be used for therapeutic administration must be sterile. Sterility is readily accomplished by filtration through sterile membranes such as 0.2 micron membranes, or by other conventional methods. Formulations typically will be stored in lyophilized form or as an aqueous solution. The pH of the preparations of this invention typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of cyclic polypeptide salts. While the preferred route of administration is by injection, other methods of administration are also anticipated such as intravenously (bolus and/or infusion), subcutaneously, intramuscularly, colonically, rectally, nasally or intraperitoneally, employing a variety of dosage forms such as suppositories, implanted pellets or small cylinders, aerosols, oral dosage formulations and topical formulations such as ointments, drops and dermal patches. The compounds of this invention are desirably incorporated into shaped articles such as implants which may employ inert materials such as biodegradable polymers or synthetic silicones, for example, Silastic, silicone rubber or other polymers commercially available.

The compounds of this invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of lipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds of this invention may also be delivered by the use of antibodies, antibody fragments, growth factors, hormones, or other targeting moieties, to which the compound molecules are coupled. The compounds of this invention may also be coupled with suitable polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxyethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the factor Xa inhibitors of this invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block

5 copolymers of hydrogels. Polymers and semipermeable polymer matrices may be formed into shaped articles, such as valves, stents, tubing, prostheses and the like.

Therapeutic compound liquid formulations generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by hypodermic injection needle.

10 Therapeutically effective dosages may be determined by either *in vitro* or *in vivo* methods. For each particular compound of the present invention, individual determinations may be made to determine the optimal dosage required. The range of therapeutically effective dosages will naturally be influenced by the route of administration, the therapeutic objectives, and the condition of the patient. For 15 injection by hypodermic needle, it may be assumed the dosage is delivered into the body's fluids. For other routes of administration, the absorption efficiency must be individually determined for each inhibitor by methods well known in pharmacology. Accordingly, it may be necessary for the therapist to titer the dosage and modify the route of administration as required to obtain the optimal therapeutic effect. The 20 determination of effective dosage levels, that is, the dosage levels necessary to achieve the desired result, will be within the ambit of one skilled in the art. Typically, applications of compound are commenced at lower dosage levels, with dosage levels being increased until the desired effect is achieved.

A typical dosage might range from about 0.001 mg/kg to about 1000 mg/kg, 25 preferably from about 0.01 mg/kg to about 100 mg/kg, and more preferably from about 0.10 mg/kg to about 20 mg/kg. Advantageously, the compounds of this invention may be administered several times daily, and other dosage regimens may also be useful.

Typically, about 0.5 to 500 mg of a compound or mixture of compounds of 30 this invention, as the free acid or base form or as a pharmaceutically acceptable salt, is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, dye, flavor etc., as called for by accepted pharmaceutical practice. The amount of active ingredient in these compositions is such that a suitable dosage in the range indicated is obtained.

35 Typical adjuvants which may be incorporated into tablets, capsules and the like are a binder such as acacia, corn starch or gelatin, and excipient such as microcrystalline cellulose, a disintegrating agent like corn starch or alginic acid, a lubricant such as magnesium stearate, a sweetening agent such as sucrose or lactose, or a flavoring agent. When a dosage form is a capsule, in addition to the

5 above materials it may also contain a liquid carrier such as water, saline, a fatty oil. Other materials of various types may be used as coatings or as modifiers of the physical form of the dosage unit. Sterile compositions for injection can be formulated according to conventional pharmaceutical practice. For example, dissolution or suspension of the active compound in a vehicle such as an oil or a synthetic fatty

10 vehicle like ethyl oleate, or into a liposome may be desired. Buffers, preservatives, antioxidants and the like can be incorporated according to accepted pharmaceutical practice.

In practicing the methods of this invention, the compounds of this invention may be used alone or in combination, or in combination with other therapeutic or

15 diagnostic agents. In certain preferred embodiments, the compounds of this inventions may be coadministered along with other compounds typically prescribed for these conditions according to generally accepted medical practice, such as anticoagulant agents, thrombolytic agents, or other antithrombotics, including platelet aggregation inhibitors, tissue plasminogen activators, urokinase, prourokinase,

20 streptokinase, heparin, aspirin, or warfarin. The compounds of this invention can be utilized in vivo, ordinarily in mammals such as primates, such as humans, sheep, horses, cattle, pigs, dogs, cats, rats and mice, or *in vitro*.

The preferred compounds of the present invention are characterized by their ability to inhibit thrombus formation with acceptable effects on classical measures of

25 coagulation parameters, platelets and platelet function, and acceptable levels of bleeding complications associated with their use. Conditions characterized by undesired thrombosis would include those involving the arterial and venous vasculature.

With respect to the coronary arterial vasculature, abnormal thrombus

30 formation characterizes the rupture of an established atherosclerotic plaque which is the major cause of acute myocardial infarction and unstable angina, as well as also characterizing the occlusive coronary thrombus formation resulting from either thrombolytic therapy or percutaneous transluminal coronary angioplasty (PTCA).

With respect to the venous vasculature, abnormal thrombus formation

35 characterizes the condition observed in patients undergoing major surgery in the lower extremities or the abdominal area who often suffer from thrombus formation in the venous vasculature resulting in reduced blood flow to the affected extremity and a predisposition to pulmonary embolism. Abnormal thrombus formation further characterizes disseminated intravascular coagulopathy commonly occurs within both

5 vascular systems during septic shock, certain viral infections and cancer, a condition
wherein there is rapid consumption of coagulation factors and systemic coagulation
which results in the formation of life-threatening thrombi occurring throughout the
microvasculature leading to widespread organ failure.

The compounds of this present invention, selected and used as disclosed
10 herein, are believed to be useful for preventing or treating a condition characterized
by undesired thrombosis, such as (a) the treatment or prevention of any
thrombotically mediated acute coronary syndrome including myocardial infarction,
unstable angina, refractory angina, occlusive coronary thrombus occurring post-
thrombolytic therapy or post-coronary angioplasty, (b) the treatment or prevention of
15 any thrombotically mediated cerebrovascular syndrome including embolic stroke,
thrombotic stroke or transient ischemic attacks, (c) the treatment or prevention of
any thrombotic syndrome occurring in the venous system including deep venous
thrombosis or pulmonary embolus occurring either spontaneously or in the setting of
malignancy, surgery or trauma, (d) the treatment or prevention of any coagulopathy
20 including disseminated intravascular coagulation (including the setting of septic
shock or other infection, surgery, pregnancy, trauma or malignancy and whether
associated with multi-organ failure or not), thrombotic thrombocytopenic purpura,
thromboangiitis obliterans, or thrombotic disease associated with heparin induced
thrombocytopenia, (e) the treatment or prevention of thrombotic complications
25 associated with extracorporeal circulation (e.g. renal dialysis, cardiopulmonary
bypass or other oxygenation procedure, plasmapheresis), (f) the treatment or
prevention of thrombotic complications associated with instrumentation (e.g. cardiac
or other intravascular catheterization, intra-aortic balloon pump, coronary stent or
cardiac valve), and (g) those involved with the fitting of prosthetic devices.

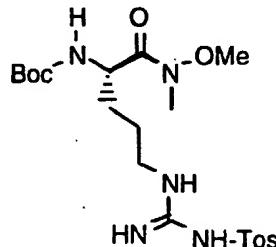
30 Anticoagulant therapy is also useful to prevent coagulation of stored whole
blood and to prevent coagulation in other biological samples for testing or storage.
Thus the compounds of this invention can be added to or contacted with any medium
containing or suspected to contain factor Xa and in which it is desired that blood
coagulation be inhibited, e.g., when contacting the mammal's blood with material
35 such as vascular grafts, stents, orthopedic prostheses, cardiac stents, valves and
prostheses, extra corporeal circulation systems and the like.

Without further description, it is believed that one of ordinary skill in the art
can, using the preceding description and the following illustrative examples, make
and utilize the compounds of the present invention and practice the claimed

5 methods. The following working examples therefore, specifically point out preferred embodiments of the present invention, and are not to be construed as limiting in any way the remainder of the disclosure.

EXAMPLE 1

10 Preparation of Boc-Arg(Tos)-N(Me)OMe

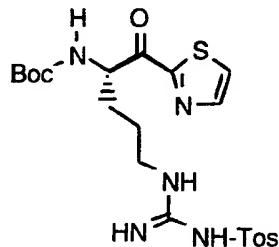


To a suspension of Boc-Arg(Tos)-OH (2 g, 4.7 mmol) in DMF (20 mL) at 0°C was added MeNHOMe.HCl (1 g, 10.3 mmol), DIEA (2 mL) and BOP (2.5 g, 5.6 mmol). The solution was stirred at 0°C for 10 h. DMF was evaporated in vacuo. The oily residue was dissolved in EtOAc (200 mL) and water (20 mL). The organic layer was washed with sat. NaHCO₃, water (20 mL), 1 M HCl (10 mL) and sat. NaCl (2 X 20 mL). The organic layer was dried over MgSO₄, filtered and evaporated to give a suspension. The suspension was filtered, washed with cold EtOAc (10 mL) and dried to give Boc-Arg(Tos)-N(Me)OMe (1.5 g, 70 % yield). FAB-MS (M+H)⁺ = 472

20

EXAMPLE 2

Preparation of Boc-Arg(Tos)-Thiazole

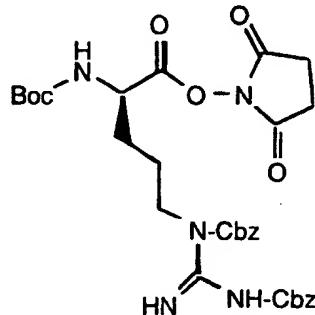


To a solution of thiazole (2.5 g, 29 mmol) in THF (25 mL) at -78°C was added n-BuLi (1.6 M in hexane, 19 mL) dropwise. The mixture was stirred for 30 min. Then a solution of Boc-Arg(Tos)-N(Me)OMe (1.7 g, 3.6 mmol) in THF (50 mL) was added to the lithiothiazole mixture at -78°C. The solution was stirred for 2 h. 1M HCl (30 mL) was added to the reaction mixture and warmed to room temperature. The mixture was extracted with EtOAc (100 mL). The organic layer was washed with sat. NaCl (30 mL), dried over MgSO₄, filtered and evaporated. The crude oily residue was

5 purified by flash column over silica gel(50% EtOAc in CH₂Cl₂) to give Boc-Arg(Tos)-Thiazole (1.5 g, 84% yield) as a white powder. DCI -MS (M+H)⁺ = 496

EXAMPLE 3

Preparation of Boc-(D)-Arg(Cbz₂)-OSu



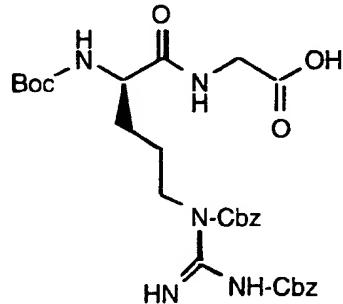
10

To a solution of Boc-(D)-Arg(Cbz₂)-OH (1 g, 1.8 mmol) in CH₂Cl₂ (10 mL) was added HOSu (466 mg, 4.06 mmol), DIEA (1 mL) and EDC (846 mg, 4.4 mmol). The solution was stirred for 48 h. The solvent was evaporated and residue was dissolved in EtOAc (50 mL) and water (10 mL). The separated organic layer was washed with sat. NaHCO₃ (10 mL), water (10 mL), 1 M HCl (10 mL) and sat. NaCl (3 X 10 mL). The organic layer was dried over MgSO₄, filtered and evaporated. The oily residue was either used directly in Example 4 without further purification or purified by flash column over silica gel (50% EtOAc in hexane) to give Boc-(D)-Arg(Cbz₂)-OSu (1 g, 85% yield).

20

EXAMPLE 4

Preparation of Boc-(D)-Arg(Cbz₂)-Gly-OH



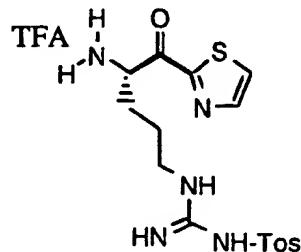
To a solution of Boc-(D)-Arg(Cbz₂)-OSu (1 g, 1.6 mmol) in dioxane (10 mL) was 25 added a solution of Gly (300 mg, 4 mmol) and NaHCO₃ (400 mg, 4.76 mmol) in water (10 mL). The solution was stirred for 24 h. Solvents were vaporized and residue was dissolved in a mixture of EtOAc (20 mL) and 1 N HCl (6 mL). The

5 separated organic layer was washed with sat. NaCl (10 mL), dried over MgSO₄, filtered and evaporated to give a solid residue which was used directly without further purification. ES-MS (M+H)⁺ = 600

EXAMPLE 5

10

Preparation of H-Arg(Tos)-Thiazole



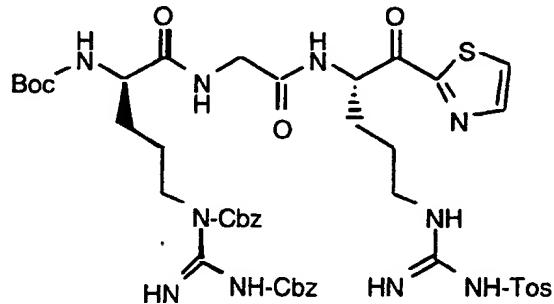
To a solution of Boc-Arg(Tos)-Thiazole (300 mg, 0.6 mmol) in CH₂Cl₂ (10 mL) at 0°C was added TFA (10 mL). The solution was stirred at 0°C for 2 h. The solvent and excess TFA were evaporated to an oily residue which was used directly without

15 further purification in Example 6.

EXAMPLE 6

Preparation of

Boc-(D)-Arg(Cbz₂)-Gly-Arg(Tos)-Thiazole

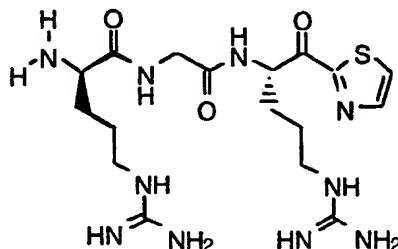


20 To a solution of Boc-Arg(Tos)-Thiazole (300 mg, 0.6 mmol) in CH₂Cl₂ (10 mL) at 0°C was added TFA (10 mL). The solution was stirred at 0°C for 2 h. The solvent and excess TFA were evaporated to an oily residue which was redissolved in CH₂Cl₂ (10 mL). The solution was cooled to 0°C, treated with DIEA (2 mL), Boc-(D)-Arg(Cbz₂)-Gly (400 mg, 0.67 mmol) and BOP (350 mg, 0.79 mmol). The solution was stirred at 0°C for 2 h. Solvent was evaporated and residue was dissolved in EtOAc (50 mL). The organic solution was washed with sat. NaHCO₃ (10 mL), water (10 mL), 1 N HCl (10 mL) and sat. NaCl (10 mL). The organic layer was dried over MgSO₄, filtered and evaporated. The oily residue was purified by

5 flash column over SiO₂ (EtOAc) to give Boc-(D)-Arg(Cbz₂)-Gly-Arg(Tos)-Thiazole
 (474 mg, 81 % yield) as a powder. ES-MS (M+H)⁺ 977

EXAMPLE 7

Preparation of H-(D)-Arg-Gly-Arg-Thiazole



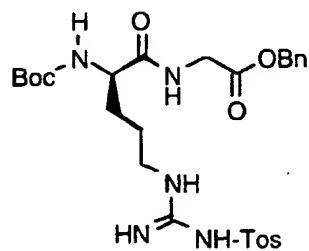
10

A 100 mg portion of Boc-(D)-Arg(Cbz₂)-Gly-Arg(Tos)-Thiazole, 1 mL of anisole and 4 drops of MeSEt were placed in HF-cleavage vessel and cooled under liquid N₂. HF (10 mL) was then condensed into the reaction mixture and stirred at 0°C for 1.25 h. HF was removed under vacuum to give a gum-like residue which was titrated with 20 mL of 50% Et₂O-hexane and the organic wash removed by filtration. The gum residue was dissolved in 30 mL of 30% aq. HOAc and filtered through the above sintered funnel. The filtrate was lyophilized to give a powder which was purified by RP-HPLC to give 28 mg (60% yield) of (D)-Arg-Gly-Arg-thiazole. FAB-MS (M+H)⁺ = 455.2

20

Example 8

Preparation of Boc-(D)-Arg(Tos)-Gly-OBn

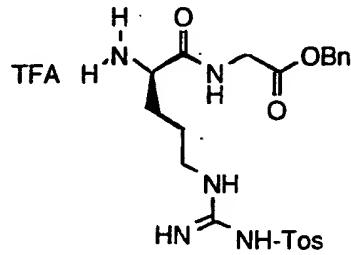


To a suspension of Boc-(D)-Arg(Tos)-OH (1 g, 2.34 mmol) in CH₂Cl₂ (10 mL) was added DIEA (1 mL) at 0°C. To the clear solution was added Gly-OBn•HCl (0.52 g, 2.58 mmol) and BOP (1.2 g, 2.8 mmol). The solution was stirred for 4 h at 0°C. Solvents were evaporated and residue was dissolved in a mixture of EtOAc (100 mL) and water (20 mL). The organic layer was washed with sat. NaHCO₃ (10 mL), water (10 mL), 1N HCl (10 mL) and sat. NaCl (3 X 10 mL), dried with MgSO₄, filtered and

5 evaporated. The solid residue was purified by column chromatography on silica gel (EtOAc) to give 1.12 g of the title compound as a powder. ES-MS $(M+H)^+$ = 576.3

EXAMPLE 9

Preparation of H-(D)-Arg(Tos)-Gly-OBn



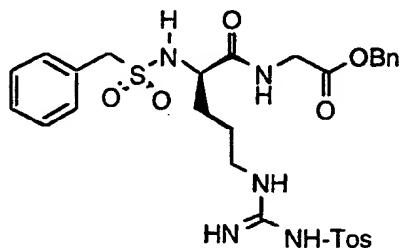
10

A 1 g portion of Boc-(D)-Arg(Tos)-Gly-OBn (1.74 mmol) was dissolved in 10 mL of CH₂Cl₂, cooled to 0°C and treated with 10 mL of TFA. The solution was stirred at 0°C for 3 h. Solvent and excess TFA were evaporated thoroughly to give the title compound as an oil which was used directly in Example 10.

15

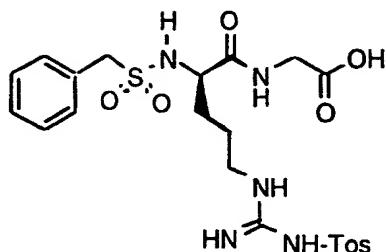
EXAMPLE 10

Preparation of BnSO₂-(D)-Arg(Tos)-Gly-OBn

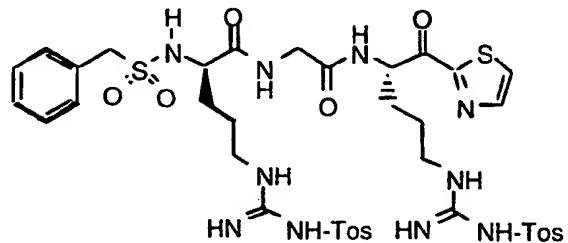


The oily residue of the compound of Example 9 was dissolved in 5 mL of DMF,
20 cooled to 0°C and neutralized with 1 mL of TEA. To the solution was added BnSO₂Cl (397 mg, 2.0 mmol) and the solution was stirred at 0°C for 3 h and 25°C for 3 h. DMF was removed and residue was dissolved in 100 mL of EtOAc and 20 mL of water. The organic layer was separated, washed with sat. NaHCO₃ (10 mL), water (10 mL), 1N HCl (10 mL) and sat. NaCl (3 X 10 mL), dried with MgSO₄, filtered
25 and evaporated. The solid residue was purified by column chromatography on silica gel (EtOAc) to give the title compound (328 mg, 30% yield) as a powder. ES-MS $(M+H)^+$ 630.5

5

EXAMPLE 11Preparation of BnSO₂-(D)-Arg(Tos)-Gly-OH

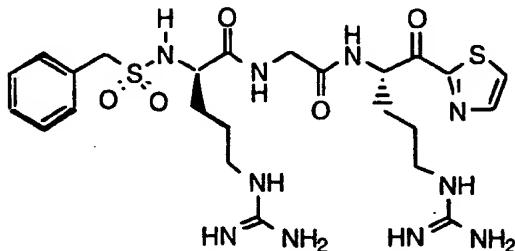
The compound of Example 10 (300 mg, 0.47 mmol) was dissolved in 10 mL of MeOH and then 10% Pd/C (150 mg) was added. The reaction was hydrogenated
 10 under normal pressure overnight, filtered through Celite, rinsed with MeOH (3 X 10 mL) and concentrated in vacuo to give the desired compound (242 mg, 84%) which was used without further purification. ES-MS (M+H)⁺ 540.0

EXAMPLE 1215 Preparation of BnSO₂-(D)-Arg(Tos)-Gly-Arg(Tos)-Thiazole

A 100 mg portion of the compound of Example 11 was coupled with 0.19 mmol of H-Arg(Tos)-thiazole (prepared following the procedure of Example 5) following the procedure as described in Example 6. RP-HPLC purification gave the title
 20 compound (110 mg, 63% yield).

FAB-MS (M+H)⁺ 917.8

5

EXAMPLE 13Preparation of BnSO₂-(D)-Arg-Gly-Arg-Thiazole

The compound of Example 13 was HF-cleaved according to the procedures described in Example 7 and purified by reversed phase HPLC to give the title
10 compound as a powder (35 mg, 47% yield). ES-MS (M+H)⁺ = 609.6

EXAMPLE 14

Evaluation of the compounds of this invention is guided by in vitro protease activity assays (see below) and in vivo studies to evaluate antithrombotic efficacy, and effects on hemostasis and hematological parameters (see Example 15 below).

The compounds of the present invention are dissolved in buffer to give solutions containing concentrations such that assay concentrations range from 0 to 100 μM. In the assays for thrombin, prothrombinase and factor Xa, a synthetic chromogenic substrate is added to a solution containing test compound and the enzyme of interest and the residual catalytic activity of that enzyme is determined spectrophotometrically. The IC₅₀ of a compound is determined from the substrate turnover. The IC₅₀ is the concentration of test compound giving 50% inhibition of the substrate turnover. The compounds of the present invention desirably have an IC₅₀ of less than 500 nM in the factor Xa assay, preferably less than 200 nM, and more preferred compounds have an IC₅₀ of about 100 nM or less in the factor Xa assay. The compounds of the present invention desirably have an IC₅₀ of less than 4.0 μM in the prothrombinase assay, preferably less than 200 nM, and more preferred compounds have an IC₅₀ of about 10 nM or less in the prothrombinase assay. The compounds of the present invention desirably have an IC₅₀ of greater than 1.0 μM in the thrombin assay, preferably greater than 10.0 μM, and more preferred compounds have an IC₅₀ of greater than 100.0 μM in the thrombin assay.

Amidolytic Assays for determining protease inhibition activity

5 The factor Xa and thrombin assays were performed at room temperature, in
0.02 M Tris-HCl buffer, pH 7.5, containing 0.15 M NaCl. The rates of hydrolysis of
the para-nitroanilide substrate S-2765 (Chromogenix) for factor Xa, and the
substrate Chromozym TH (Boehringer Mannheim) for thrombin following
preincubation of the enzyme with inhibitor for 5 minutes at room temperature, and
10 were determined using the Softmax 96-well plate reader (Molecular Devices),
monitored at 405 nm to measure the time dependent appearance of p-nitroaniline.

The prothrombinase inhibition assay was performed in a plasma free system
with modifications to the method described by Sinha, U. *et al.*, Thromb. Res., 75,
427-436 (1994). Specifically, the activity of the prothrombinase complex was
15 determined by measuring the time course of thrombin generation using the p-
nitroanilide substrate Chromozym TH. The assay consists of preincubation (5
minutes) of selected compounds to be tested as inhibitors with the complex formed
from factor Xa (0.5 nM), factor Va (2 nM), phosphatidyl serine:phosphatidyl choline
(25:75, 20 μ M) in 20 mM Tris-HCl buffer, pH 7.5, containing 0.15 M NaCl, 5 mM
20 CaCl₂ and 0.1% bovine serum albumin. Aliquots from the complex-inhibitor mixture
were added to prothrombin (1 nM) and Chromozym TH (0.1 mM). The rate of
substrate cleavage was monitored at 405 nm for two minutes. Eight different
concentrations of inhibitor were assayed in duplicate. A standard curve of thrombin
generation by an equivalent amount of untreated complex was used for
25 determination of percent inhibition.

EXAMPLE 15

A series of studies were accomplished in rabbits to evaluate the antithrombotic
efficacy, and effects on hemostasis and hematological parameters of the compound (D)-
30 Arg-Gly-Arg-thiazole.

Antithrombotic Efficacy in a Rabbit Model of Venous Thrombosis

A rabbit deep vein thrombosis model as described by Hollenbach, S. *et al.*,
Thromb. Haemost. 71, 357-362 (1994), was used to determine the in-vivo antithrombotic
activity of the test compounds. Rabbits were anesthetized with I.M. injections of
35 Ketamine, Xylazine, and Acepromazine cocktail. A standardized protocol consisted of
insertion of a thrombogenic cotton thread and copper wire apparatus into the abdominal
vena cava of the anesthetized rabbit. A non-occlusive thrombus was allowed to develop in
the central venous circulation and inhibition of thrombus growth was used as a measure of
the antithrombotic activity of the studied compounds. Test agents or control saline were

5 administered through a marginal ear vein catheter. A femoral vein catheter was used for blood sampling prior to and during steady state infusion of test compound. Initiation of thrombus formation begins immediately after advancement of the cotton thread apparatus into the central venous circulation. Test compounds were administered from time = 30 min to time = 150 min at which the experiment was terminated. The rabbits were
 10 euthanized and the thrombus excised by surgical dissection and characterized by weight and histology. Blood samples were analyzed for changes in hematological and coagulation parameters.

Effects of (D)-Arg-Gly-Arg-thiazole in Rabbit Venous Thrombosis model

Administration of (D)-Arg-Gly-Arg-thiazole in the rabbit venous thrombosis model
 15 demonstrated antithrombotic efficacy at the higher doses evaluated. There was no significant effect of the compound on the aPTT and PT prolongation with the highest dose (100 µg/kg + 2.57 µg/kg/min)(see Table 2). (D)-Arg-Gly-Arg-thiazole had no significant effects on hematological parameters as compared to saline controls (see Table 3).

20 TABLE 2 - ANTITHROMBOTIC EFFECTS OF (D)-Arg-Gly-Arg-thiazole IN RABBITS

	Dose Regimen baseline-- (µg/kg + µg/kg/min)	% Inhibition of Thrombosis		-fold increase over	
		n#	aPTT	PT	
25	saline control 0.00	6	0.0	0.96 ± 0.01	1.00 ±
	50 + 1.28 0.00	6	-7.84	1.00 ± 0.03	1.00 ±
	75 + 1.93 0.00	5	42.95	1.02 ± 0.03	1.00 ±
30	100 + 2.57 0.00	6	117.72	1.08 ± 0.02	0.83 ±

All measurements are an average of all samples after steady state administration of vehicle or (D)-Arg-Gly-Arg-thiazole. Values are expressed as mean ± SD.

5 TABLE 3 - EFFECTS OF (D)-Arg-Gly-Arg-thiazole ON HEMATOLOGICAL PARAMETERS

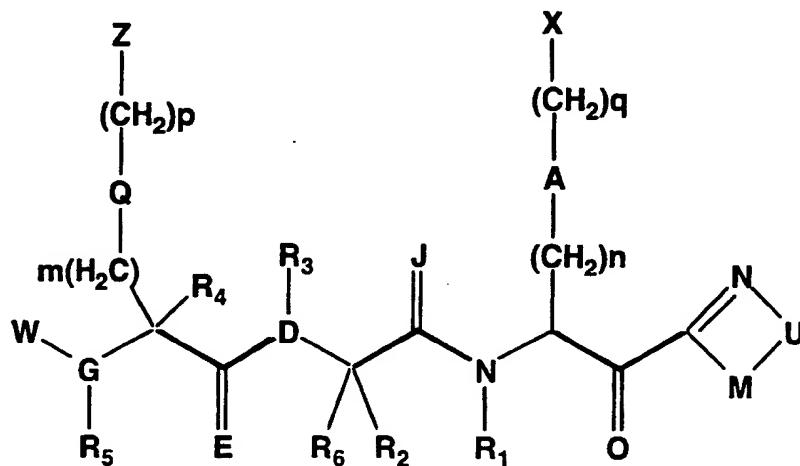
Dose Regimen ($\mu\text{g/kg} + \mu\text{g/kg/min}$)	n#	RBC $\times 10^6/\mu\text{L}$	WBC $\times 10^3/\mu\text{L}$	PLT $\times 10^3/\mu\text{L}$	Hct %
saline control	6	5.96 \pm 0.66	3.38 \pm 0.83	338 \pm 77	35.2 \pm
10 2.81					
50 + 1.28	6	5.66 \pm 0.25	3.70 \pm 0.50	349 \pm 75	36.9 \pm
3.90					
75 + 1.93	5	5.74 \pm 0.42	4.23 \pm 0.99	413 \pm 64	35.3 \pm
3.01					
15 100 + 2.57	6	6.08 \pm 0.42	4.15 \pm 0.52	439 \pm 61	35.5 \pm
1.01					

All measurements are an average of samples after steady state administration of vehicle or

(D)-Arg-Gly-Arg-thiazole. Values are mean \pm SD.

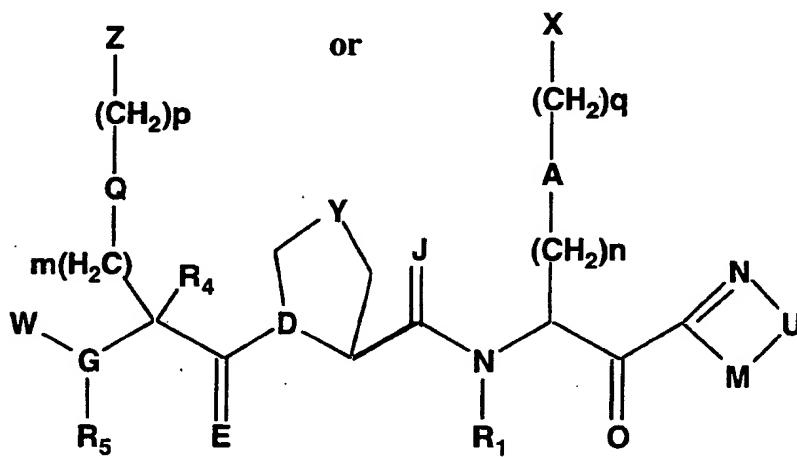
5 WHAT IS CLAIMED IS:

1. A compound represented by the formula:



10

or



wherein:

m = 0,1,2,3,4;

n = 0,1,2,3,4;

15

p = 0,1,2,3,4;

q = 0,1,2,3,4;

Y = NH, S, O, CH₂, CH-OH, CH₂CH₂, C=O;A = piperdinyl, pyrrolidinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, C₃₋₆heteroaryl, or is absent;

20

R₁ = H or C₁₋₃alkyl;J = O or H₂;

5 R₂ = H or C₁₋₃alkyl;
 D = N, CH, NCH₂, NCH₂CH₂, CHCH₂;
 R₃ = H or C₁₋₃alkyl;
 E = O or H₂;
 R₄ = H or CH₃;

10 M = NH, N-CH₃, O, S, SO, SO₂, CH₂ or is absent;
 Q = piperdinyl, pyrrolidinyl, C₃₋₈ cycloalkyl, phenyl, substituted
 phenyl, naphthyl, pyridyl, or is absent;
 G = N, CH, or is H;
 R₅ = H or C₁₋₃ alkyl or is absent if G is H;

15 R₆ = H or CH₃;
 U = is selected from a group consisting of

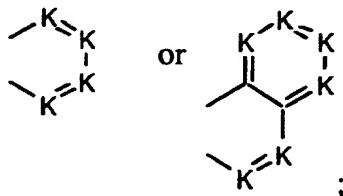
R₇

; ; ;

20 where n = 0-4; R₇ and R₈ are independently selected from a
 group consisting of H, C₁₋₁₀alkyl, aryl, arylalkyl, halogen,
 nitro, an amino group of formula -NR₉R₁₀, an acylamino
 group of formula -NHCOR₁₁, hydroxy, an acyloxy group of
 formula -OCOR₁₂, C₁₋₄alkyloxy, C₁₋₄alkyl, trifluoromethyl,
 carboxy, cyano, phenyl, aromatic heterocyclic group as
 defined herein below, C₁₋₄alkyloxycarbonyl, an aminocarbonyl
 group of formula CONR₁₃R₁₄, sulfo, sulfonamido of formula
 SO₂NR₁₅R₁₆ and C₁₋₆ hydroxyalkyl; wherein R₉, R₁₀, R₁₁,
 R₁₂, R₁₃, R₁₄, R₁₅, R₁₆ are the same or different and = H,

25 C₁₋₆ alkyl, C₁₋₃arylalkyl or aryl and if M is absent:

30 C₁₋₆ alkyl, C₁₋₃arylalkyl or aryl and if M is absent:



5

 $K = C$ or N ;

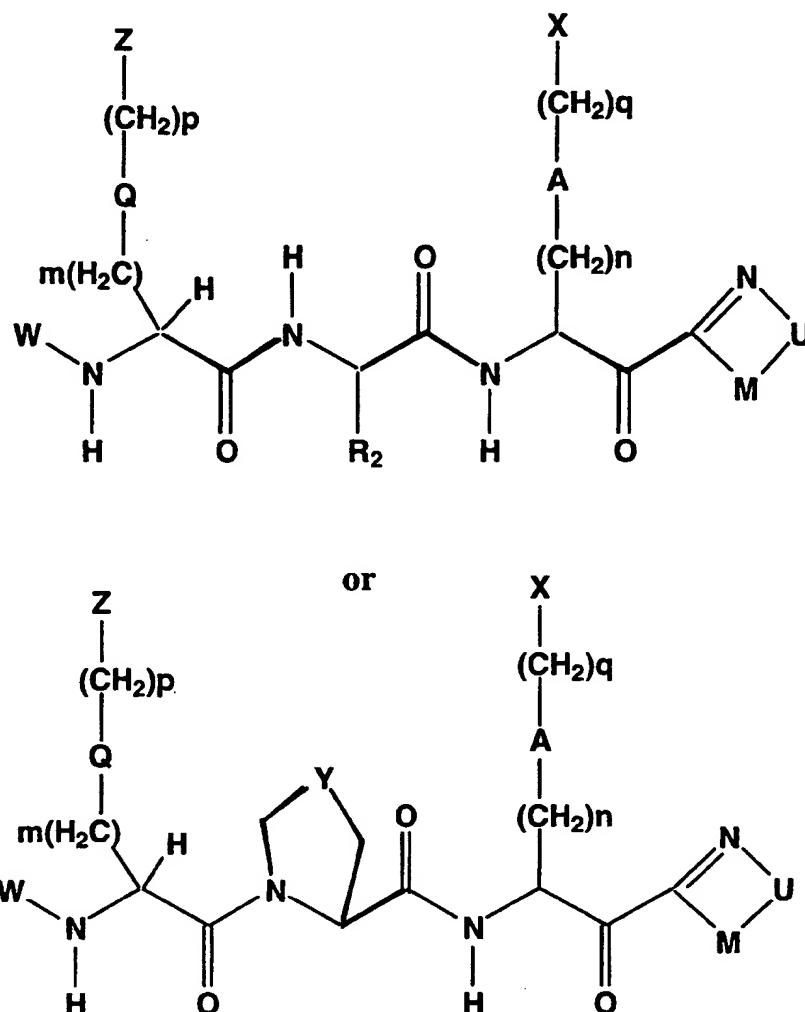
W = H, arylacyl, heteroarylacyl, arylC₁₋₃alkylsulfonyl, arylsulfonyl, substituted arylsulfonyl, arylC₁₋₄alkenylsulfonyl, C₁₋₈alkylsulfonyl, heteroarylC₁₋₃alkylsulfonyl, heteroarylsulfonyl, aryloxycarbonyl, C₁₋₆alkyloxycarbonyl, arylC₁₋₃alkylaminocarbonyl, HOOC-C₀₋₃alkylcarbonyl, or is absent if G is H;

X = H, C₁₋₃alkyl, NR'R'', NH-C(NR'R'')=NH, NH-C(NHR')=NR'', NH-C(R')=NR'', S-C(NR'R'')=NH, S-C(NHR')=NR'', C(NR'R'')=NH, C(NHR')=NR'' or CR'=NR''; where: R', R'' are the same or different and = H, C₁₋₆alkyl, C₁₋₃aryllalkyl, aryl or where R'R'' forms a cyclic ring containing (CH₂)_p where p=2-5, with the proviso that when X is H or C₁₋₃alkyl, then A must contain at least one N atom;

Z = H, C₁₋₃alkyl, NR'R'', NH-C(NR'R'')=NH, NH-C(NHR')=NR'', NH-C(R')=NR'', S-C(NR'R'')=NH, S-C(NHR')=NR'', C(NR'R'')=NH, C(NHR')=NR'' or CR'=NR''; where: R', R'' are the same or different and = H, C₁₋₆alkyl, C₁₋₃aryllalkyl, aryl or where R'R'' forms a cyclic ring containing (CH₂)_p where p=2-5, with the proviso that when Z is H or C₁₋₃alkyl, then Q must contain at least one N atom;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

2. The compound of claim 1, having the formula:



5

wherein:

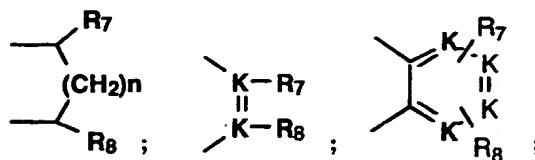
10

 $m = 0, 1, 2, 3, 4;$ $n = 0, 1, 2, 3, 4;$ $p = 0, 1, 2, 3, 4;$ $q = 0, 1, 2, 3, 4;$ $Y = \text{NH, S, O, CH}_2, \text{CH-OH, CH}_2\text{CH}_2;$ $A = \text{piperdinyl, pyrrolidinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, C}_3\text{-6heteroaryl, or is absent;}$ $M = \text{NH, N-CH}_3, \text{O, S, SO}_2\text{CH}_2 \text{ or is absent;}$

15

 $Q = \text{piperdinyl, pyrrolidinyl, C}_3\text{-8 cycloalkyl, phenyl, substituted phenyl, naphthyl, pyridyl, or is absent}$ $U = \text{is selected from a group consisting of}$

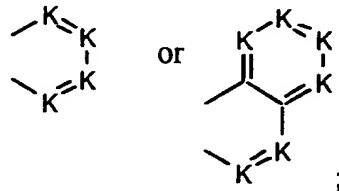
5



10

where $n = 0-4$; R_7 and R_8 are independently selected from a group consisting of H, C₁₋₁₀alkyl, aryl, arylalkyl, halogen, nitro, an amino group of formula -NR₉R₁₀, an acylamino group of formula -NHCOR₁₁, hydroxy, an acyloxy group of formula -OCOR₁₂, C₁₋₄alkyloxy, C₁₋₄alkyl, trifluoromethyl, carboxy, cyano, phenyl, aromatic heterocyclic group as defined herein below, C₁₋₄alkyloxycarbonyl, an aminocarbonyl group of formula CONR₁₃R₁₄, sulfo, sulfonamido of formula SO₂NR₁₅R₁₆ and C₁₋₆hydroxalkyl; wherein R₉, R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆ are the same or different and = H, C₁₋₆ alkyl, C₁₋₃arylalkyl or aryl; and if M is absent:

15



20

$K = C$ or N ;
 $W = H$, arylacyl, heteroarylacyl, arylC₁₋₃alkylsulfonyl, arylsulfonyl, substituted arylsulfonyl, arylC₁₋₄alkenylsulfonyl, C₁₋₈alkylsulfonyl, heteroarylC₁₋₃alkylsulfonyl, heteroarylalkylsulfonyl, aryloxycarbonyl, C₁₋₆alkyloxycarbonyl, arylC₁₋₃alkyloxycarbonyl, arylaminocarbonyl, C₁₋₆alkylaminocarbonyl, arylC₁₋₃alkylaminocarbonyl, HOOC-CO-3alkylcarbonyl, or is absent if G is H;

25

$X = H$, C₁₋₃alkyl, NR'R'', NH-C(NR'R'')=NH, NH-C(NHR')=NR'', NH-C(R')=NR'', S-C(NR'R'')=NH, S-C(NHR')=NR'', C(NR'R'')=NH, C(NHR')=NR'' or CR'=NR''; where: R', R'' are the same or different and = H, C₁₋₆alkyl, C₁₋₃arylalkyl, aryl or where R'R'' forms a cyclic ring containing (CH₂)_p where p=2-5, with the

30

5 proviso that when X is H or C₁₋₃alkyl, then A must contain at least one N atom;
Z = H, C₁₋₃alkyl, NR'R'', NH-C(NR'R'')=NH, NH-C(NHR')=NR'', NH-C(R')=NR'', S-C(NR'R'')=NH, S-C(NHR')=NR'', C(NR'R'')=NH, C(NHR')=NR'' or CR'=NR''; where: R', R'' are the same or different and = H, C₁₋₆alkyl, C₁₋₃arylalkyl, aryl or where R'R'' forms a cyclic ring containing (CH₂)_p where p=2-5, with the proviso that when Z is H or C₁₋₃alkyl, then Q must contain at least one N atom;

10 and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

3. The compound of claim 1, having an IC₅₀ for Factor Xa of less than about 200 nM.

20 4. The compound of claim 1, having an IC₅₀ for prothrombinase of less than about 2.0 μM.

5. The compound of claim 1, having an IC₅₀ for thrombin of greater than about 1.0 μm.

25 6. A compound selected from a group consisting of:
H-D-Arg-Gly-Arg-thiazole
BnSO₂-(D)-Arg-Gly-Arg-thiazole
PhCH₂CH₂-SO₂-(D)-Arg-Gly-Arg-Thiazole
30 C₆H₁₁CH₂CH₂SO₂-(D)-Arg-Gly-Arg-Thiazole
Me₃C-C₆H₄SO₂-(D)-Arg-Gly-Arg-Thiazole
C₁₀H₇SO₂-(D)-Arg-Gly-Arg-Thiazole
Me₃SiCH₂CH₂CH₂SO₂-(D)-Arg-Gly-Arg-Thiazole
BnSO₂-(D)-4-Apa-Gly-Arg-Thiazole
35 BnSO₂-(D)-4-Gpa-Gly-Arg-Thiazole
BnSO₂-(D)-Acp-Gly-Arg-Thiazole
BnSO₂-(D)-homo-Lys-Gly-Arg-Thiazole

5 BnSO₂-(D)-Arg-Sar-Arg-Thiazole
 BnSO₂-(D)-Arg-Pro-Arg-Thiazole
 BnSO₂-(D)-Arg-Gly-4-Acg-Thiazole
 BnSO₂-(D)-Arg-Gly-(3-NH₂-Phe)-Thiazole
 BnSO₂-(D)-Arg-Gly-(4-NH₂-Phe)-Thiazole
10 BnSO₂-(D)-Arg-Gly-Gpa-Thiazole
 Boc-D-(2,3-Dap)-Gly-Arg-Thiazole
 Boc-D-(2,4-Dab)-Gly-Arg-Thiazole
 g-Abu-Gly-Arg-Thiazole
 Boc-D-Orn-Gly-Arg-Thiazole
15 Boc-D-homoLys-Gly-Arg-Thiazole
 Boc-Bag-Gly-Arg-Thiazole
 Boc-D-4-Gpa-Gly-Arg-Thiazole
 Boc-D-3-Gpa-Gly-Arg-Thiazole
 Boc-D-4-Apa-Gly-Arg-Thiazole
20 Boc-D-3-Apa-Gly-Arg-Thiazole
 Boc-D-4-Acg-Gly-Arg-Thiazole
 Boc-D-(4-NH₂Phe)-Gly-Arg-Thiazole
 Boc-D-(3-NH₂Phe)-Gly-Arg-Thiazole
 BnSO₂-D-(2,3-Dap)-Gly-Arg-Thiazole
25 BnSO₂-D-(2,4-Dab)-Gly-Arg-Thiazole
 BnSO₂-D-Orn-Gly-Arg-Thiazole
 BnSO₂-Bag-Gly-Arg-Thiazole
 BnSO₂-D-3-Gpa-Gly-Arg-Thiazole
 BnSO₂-D-3-Apa-Gly-Arg-Thiazole
30 BnSO₂-D-(4-NH₂Phe)-Gly-Arg-Thiazole
 BnSO₂-D-(3-NH₂Phe)-Gly-Arg-Thiazole
 BnSO₂-D-(2,3-Dap)-Gly-Arg-Benzothiazole
 BnSO₂-D-(2,4-Dab)-Gly-Arg-Benzothiazole
 BnSO₂-D-Orn-Gly-Arg-Benzothiazole
35 BnSO₂-Bag-Gly-Arg-Benzothiazole
 BnSO₂-D-4-Gpa-Gly-Arg-Benzothiazole
 BnSO₂-D-3-Gpa-Gly-Arg-Benzothiazole

5 BnSO₂-D-4-Apa-Gly-Arg-Benzothiazole
 BnSO₂-D-3-Apa-Gly-Arg-Benzothiazole
 BnSO₂-D-4-Acg-Gly-Arg-Benzothiazole
 BnSO₂-D-(4-NH₂Phe)-Gly-Arg-Benzothiazole
 BnSO₂-D-(3-NH₂Phe)-Gly-Arg-Benzothiazole

10 BnSO₂-D-Arg-Gly-(2,4-Dab)-Benzothiazole
 BnSO₂-D-Arg-Gly-(homoLys)-Benzothiazole
 BnSO₂-D-Arg-Gly-(4-Gpa)-Benzothiazole
 BnSO₂-D-Arg-Gly-(3-Gpa)-Benzothiazole
 BnSO₂-D-Arg-Gly-(4-Apa)-Benzothiazole

15 BnSO₂-D-Arg-Gly-(3-Apa)-Benzothiazole
 BnSO₂-D-Arg-Gly-(4-NH₂Phe)-Benzothiazole
 BnSO₂-D-Arg-Gly-(3-NH₂Phe)-Benzothiazole
 Me₃SiCH₂CH₂CH₂SO₂-(D)-Arg-Gly-Arg-Benzothiazole
 BnSO₂-(D)-homo-Lys-Gly-Arg-Benzothiazole

20 BnSO₂-(D)-homo-Lys-Gly-Arg-Benzoxazole
 PhCH₂CH₂SO₂-(D)-Arg-Gly-Arg-Benzothiazole
 BnSO₂-(D)-Arg-Sar-Arg-Benzothiazole
 BnSO₂-(D)-Arg-Pro-Arg-Benzothiazole
 BnSO₂-(D)-Arg-Gly-Acg-Benzothiazole

25 BnSO₂-(D)-Arg-Gly-Arg-Benzothiazole
 PhCH₂CH₂SO₂-(D)-Arg-Gly-4-Acg-Benzothiazole
 BnSO₂-(D)-Arg-Gly-Arg-Oxazole
 Boc-D-(2,3-Dap)-Gly-Arg-Oxazole
 Boc-D-(2,4-Dab)-Gly-Arg-Oxazole

30 g-Abu-Gly-Arg-Oxazole
 Boc-D-Orn-Gly-Arg-Oxazole
 Boc-D-homoLys-Gly-Arg-Oxazole
 Boc-Bag-Gly-Arg-Oxazole
 Boc-D-4-Gpa-Gly-Arg-Oxazole

35 Boc-D-3-Gpa-Gly-Arg-Oxazole
 Boc-D-4-Apa-Gly-Arg-Oxazole
 Boc-D-3-Apa-Gly-Arg-Oxazole

5 Boc-D-4-Acg-Gly-Arg-Oxazole
 Boc-D-(4-NH₂Phe)-Gly-Arg-Oxazole
 Boc-D-(3-NH₂Phe)-Gly-Arg-Oxazole
 BnSO₂-D-(2,3-Dap)-Gly-Arg-Oxazole
 BnSO₂-D-(2,4-Dab)-Gly-Arg-Oxazole

10 BnSO₂-D-Orn-Gly-Arg-Oxazole
 BnSO₂-Bag-Gly-Arg-Oxazole
 BnSO₂-D-3-Gpa-Gly-Arg-Oxazole
 BnSO₂-D-3-Apa-Gly-Arg-Oxazole
 BnSO₂-D-(4-NH₂Phe)-Gly-Arg-Oxazole

15 BnSO₂-D-(3-NH₂Phe)-Gly-Arg-Oxazole
 BnSO₂-D-(2,3-Dap)-Gly-Arg-Oxazole
 BnSO₂-D-(2,4-Dab)-Gly-Arg-Oxazole
 BnSO₂-D-Orn-Gly-Arg-Oxazole
 BnSO₂-Bag-Gly-Arg-Oxazole

20 BnSO₂-D-4-Gpa-Gly-Arg-Oxazole
 BnSO₂-D-3-Gpa-Gly-Arg-Oxazole
 BnSO₂-D-4-Apa-Gly-Arg-Oxazole
 BnSO₂-D-3-Apa-Gly-Arg-Oxazole
 BnSO₂-D-4-Acg-Gly-Arg-Oxazole

25 BnSO₂-D-(4-NH₂Phe)-Gly-Arg-Oxazole
 BnSO₂-D-(3-NH₂Phe)-Gly-Arg-Oxazole
 BnSO₂-D-Arg-Gly-(2,4-Dab)-Oxazole
 BnSO₂-D-Arg-Gly-(homoLys)-Oxazole
 BnSO₂-D-Arg-Gly-(4-Gpa)-Oxazole

30 BnSO₂-D-Arg-Gly-(3-Gpa)-Oxazole
 BnSO₂-D-Arg-Gly-(4-Apa)-Oxazole
 BnSO₂-D-Arg-Gly-(3-Apa)-Oxazole
 BnSO₂-D-Arg-Gly-(4-NH₂Phe)-Oxazole
 BnSO₂-D-Arg-Gly-(3-NH₂Phe)-Oxazole

35 BnSO₂-D-(2,3-Dap)-Gly-Arg-Benzoxazole
 BnSO₂-D-(2,4-Dab)-Gly-Arg-Benzoxazole

5 BnSO₂-D-Orn-Gly-Arg-Benzoxazole
 BnSO₂-Bag-Gly-Arg-Benzoxazole
 BnSO₂-D-4-Gpa-Gly-Arg-Benzoxazole
 BnSO₂-D-3-Gpa-Gly-Arg-Benzoxazole
 BnSO₂-D-4-Apa-Gly-Arg-Benzoxazole
10 BnSO₂-D-3-Apa-Gly-Arg-Benzoxazole
 BnSO₂-D-4-Acg-Gly-Arg-Benzoxazole
 BnSO₂-D-(4-NH₂Phe)-Gly-Arg-Benzoxazole
 BnSO₂-D-(3-NH₂Phe)-Gly-Arg-Benzoxazole
 BnSO₂-D-Arg-Gly-(2,4-Dab)-Benzoxazole
15 BnSO₂-D-Arg-Gly-(homoLys)-Benzoxazole
 BnSO₂-D-Arg-Gly-(4-Gpa)-Benzoxazole
 BnSO₂-D-Arg-Gly-(3-Gpa)-Benzoxazole
 BnSO₂-D-Arg-Gly-(4-Apa)-Benzoxazole
 BnSO₂-D-Arg-Gly-(3-Apa)-Benzoxazole
20 BnSO₂-D-Arg-Gly-(4-NH₂Phe)-Benzoxazole
 BnSO₂-D-Arg-Gly-(3-NH₂Phe)-Benzoxazole
 Me₃SiCH₂CH₂CH₂SO₂-(D)-Arg-Gly-Arg-Benzoxazole
 BnSO₂-(D)-homo-Lys-Gly-Arg-Benzoxazole
 BnSO₂-(D)-homo-Lys-Gly-Arg-Benzoxazole
25 PhCH₂CH₂SO₂-(D)-Arg-Gly-Arg-Benzoxazole
 BnSO₂-(D)-Arg-Sar-Arg-Benzoxazole
 BnSO₂-(D)-Arg-Pro-Arg-Benzoxazole
 BnSO₂-(D)-Arg-Gly-Acg-Benzoxazole
 BnSO₂-(D)-Arg-Gly-Arg-Benzoxazole
30 PhCH₂CH₂SO₂-(D)-Arg-Gly-4-Acg-Benzoxazole
 BnSO₂-(D)-Arg-Gly-Arg-Benzoxazole
 BnSO₂-(D)-Arg-Gly-Acg-Benzoxazole
 PhCH₂CH₂SO₂-(D)-Arg-Gly-Arg-Benzoxazole
 PhCH₂CH₂SO₂-(D)-Arg-Gly-4-Acg-Benzoxazole
35 Me₃SiCH₂CH₂CH₂SO₂-(D)-Arg-Gly-Arg-Benzoxazole
 BnSO₂-(D)-Arg-Gly-Arg-Oxazoline

5 Boc-D-(2,3-Dap)-Gly-Arg-Oxazoline
 Boc-D-(2,4-Dab)-Gly-Arg-Oxazoline
 g-Abu-Gly-Arg-Oxazoline
 Boc-D-Orn-Gly-Arg-Oxazoline
 Boc-D-homoLys-Gly-Arg-Oxazoline

10 Boc-Bag-Gly-Arg-Oxazoline
 Boc-D-4-Gpa-Gly-Arg-Oxazoline
 Boc-D-3-Gpa-Gly-Arg-Oxazoline
 Boc-D-4-Apa-Gly-Arg-Oxazoline
 Boc-D-3-Apa-Gly-Arg-Oxazoline

15 Boc-D-4-Acg-Gly-Arg-Oxazoline
 Boc-D-(4-NH₂Phe)-Gly-Arg-Oxazoline
 Boc-D-(3-NH₂Phe)-Gly-Arg-Oxazoline
 BnSO₂-D-(2,3-Dap)-Gly-Arg-Oxazoline
 BnSO₂-D-(2,4-Dab)-Gly-Arg-Oxazoline

20 BnSO₂-D-Orn-Gly-Arg-Oxazoline
 BnSO₂-Bag-Gly-Arg-Oxazoline
 BnSO₂-D-3-Gpa-Gly-Arg-Oxazoline
 BnSO₂-D-3-Apa-Gly-Arg-Oxazoline
 BnSO₂-D-(4-NH₂Phe)-Gly-Arg-Oxazoline

25 BnSO₂-D-(3-NH₂Phe)-Gly-Arg-Oxazoline
 BnSO₂-D-(2,3-Dap)-Gly-Arg-Oxazoline
 BnSO₂-D-(2,4-Dab)-Gly-Arg-Oxazoline
 BnSO₂-D-Orn-Gly-Arg-Oxazoline
 BnSO₂-Bag-Gly-Arg-Oxazoline

30 BnSO₂-D-4-Gpa-Gly-Arg-Oxazoline
 BnSO₂-D-3-Gpa-Gly-Arg-Oxazoline
 BnSO₂-D-4-Apa-Gly-Arg-Oxazoline
 BnSO₂-D-3-Apa-Gly-Arg-Oxazoline
 BnSO₂-D-4-Acg-Gly-Arg-Oxazoline

35 BnSO₂-D-(4-NH₂Phe)-Gly-Arg-Oxazoline
 BnSO₂-D-(3-NH₂Phe)-Gly-Arg-Oxazoline
 BnSO₂-D-Arg-Gly-(2,4-Dab)-Oxazoline

5 BnSO₂-D-Arg-Gly-(homoLys)-Oxazoline
 BnSO₂-D-Arg-Gly-(4-Gpa)-Oxazoline
 BnSO₂-D-Arg-Gly-(3-Gpa)-Oxazoline
 BnSO₂-D-Arg-Gly-(4-Apa)-Oxazoline
 BnSO₂-D-Arg-Gly-(3-Apa)-Oxazoline
10 BnSO₂-D-Arg-Gly-(4-NH₂Phe)-Oxazoline
 BnSO₂-D-Arg-Gly-(3-NH₂Phe)-Oxazoline
 BnSO₂-(D)-Arg-Gly-Arg-Imidazole
 BnSO₂-(D)-Arg-Gly-Arg-Pyridine
 BnSO₂-(D)-Arg-Gly-Arg-2-(1-methyl-tetrazole)
15 BnSO₂-(D)-Arg-Gly-Arg-2-(4-methyl-tetrazole)
 MeSO₂-(D)-Arg-Gly-Arg-Thiazole
 BnSO₂-(D)-(4-H₂NCH₂-Phe)-Gly-Arg-Thiazole
 BnSO₂-(D)-(4-H₂NCH₂-Phg)-Gly-Arg Thiazole
 BnSO₂-(D)-(3-Py-Ala)-Gly-Arg-Thiazole
20 BnSO₂-(D)-(3-Me-3-Py-Ala)-Gly-Arg-Thiazole
 BnSO₂-(D)-(3-Pip-Ala)-Gly-Arg-Thiazole
 BnSO₂-(D)-(4-Pip-Ala)-Gly-Arg-Thiazole
 BnSO₂-(D)-(3-Amidino-3-Pip-Ala)-Gly-Arg-Thiazole

25 7. The compound of Claim 6 selected from the group consisting
 of:
 H-D-Arg-Gly-Arg-Thiazole
 BnSO₂-(D)-Arg-Gly-Arg-Thiazole
 MeSO₂-(D)-Arg-Gly-Arg-Thiazole
30 BnSO₂-(D)-Arg-Gly-Arg-Benzoxazole
 BnSO₂-(D)-(3-Pip-Ala)-Gly-Arg-Thiazole
 BnSO₂-(D)-(4-Pip-Ala)-Gly-Arg-Thiazole
 BnSO₂-(D)-(3-Amidino-3-Pip-Ala)-Gly-Arg-Thiazole

35 8. A pharmaceutical composition for preventing or treating a condition in a
 mammal characterized by undesired thrombosis comprising a therapeutically

5 acceptable carrier and a therapeutically effective amount of a compound of claim 1, 2, or 6.

9. A method for preventing or treating a condition in a mammal characterized by undesired thrombosis comprising administering to said mammal a

10 therapeutic effective amount of a compound of claim 1, 2, or 6.

10. The method of claim 9, wherein the condition is selected from the group consisting of:
acute coronary syndrome, myocardial infarction, unstable angina, refractory
15 angina, occlusive coronary thrombus occurring post-thrombolytic therapy or post-coronary angioplasty, a thrombotically mediated cerebrovascular syndrome, embolic stroke, thrombotic stroke, transient ischemic attacks, venous thrombosis, deep venous thrombosis, pulmonary embolus, coagulopathy, disseminated intravascular coagulation, thrombotic
20 thrombocytopenic purpura, thromboangiitis obliterans, thrombotic disease associated with heparin-induced thrombocytopenia, thrombotic complications associated with extracorporeal circulation, thrombotic complications associated with instrumentation such as cardiac or other intravascular catheterization, intra-aortic balloon pump, coronary stent or cardiac valve,
25 and conditions requiring the fitting of prosthetic devices.

11. A method for inhibiting the coagulation biological samples, comprising the administration of a compound of claim 1, 2 or 6.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 96/09290

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07K5/06 A61K38/05

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 648 780 (BRISOL-MYERS SQUIBB COMP., PRINCETON, NJ, US) 19 April 1995 pages 3 - 5, claims, table ---	1-11
Y	US,A,5 153 176 (NITTO BOSEKI CO, FUKUSHIMA, JP) 6 October 1992 cited in the application whole document, especially example 21 ---	1-11
P,Y	CHEMICAL ABSTRACTS, vol. 124, no. 23, 1996, page 1296 XP002017940 OKONOGI K. ET AL.: "Preparation of amino acid and peptide N-heterocyclcarbonylalkylamides as thrombin inhibitors, 124:317893a" whole abstract --- -/-	1-11

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

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1

Date of the actual completion of the international search

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Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 96/09290

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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P,Y	US,A,5 523 308 (COSTANZO J.M. , IVYLAND, PA, MARYANOFF B.E., NEW HOPE, PA) 4 June 1996 whole document ---	1-11
P,Y	J.MED.CHEM., vol. 39, no. 16, 1996, US, pages 3039-43, XP002017921 COSTANZO ET AL.: "Potent Thrombin Inhibitors that probe the S1'Subsite: Tripeptide Transition State Analogues based on a Heterocycle-Activated Carbonyl Group" whole publication ---	1-11
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Information on patent family members

International Application No

PCT/US 96/09290

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		AU-A-	4250896	10-07-96
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